© THE QUEEN'S PRINTER FOR ONTARIO
2000

REPRODUCED WITH PERMISSION

L'IMPRIMEUR DE LA REINE POUR L'ONTARIO

REPRODUIT AVEC PERMISSION

micromedia
a division of IHS Canada

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

Published Fall 2000

1st Edition

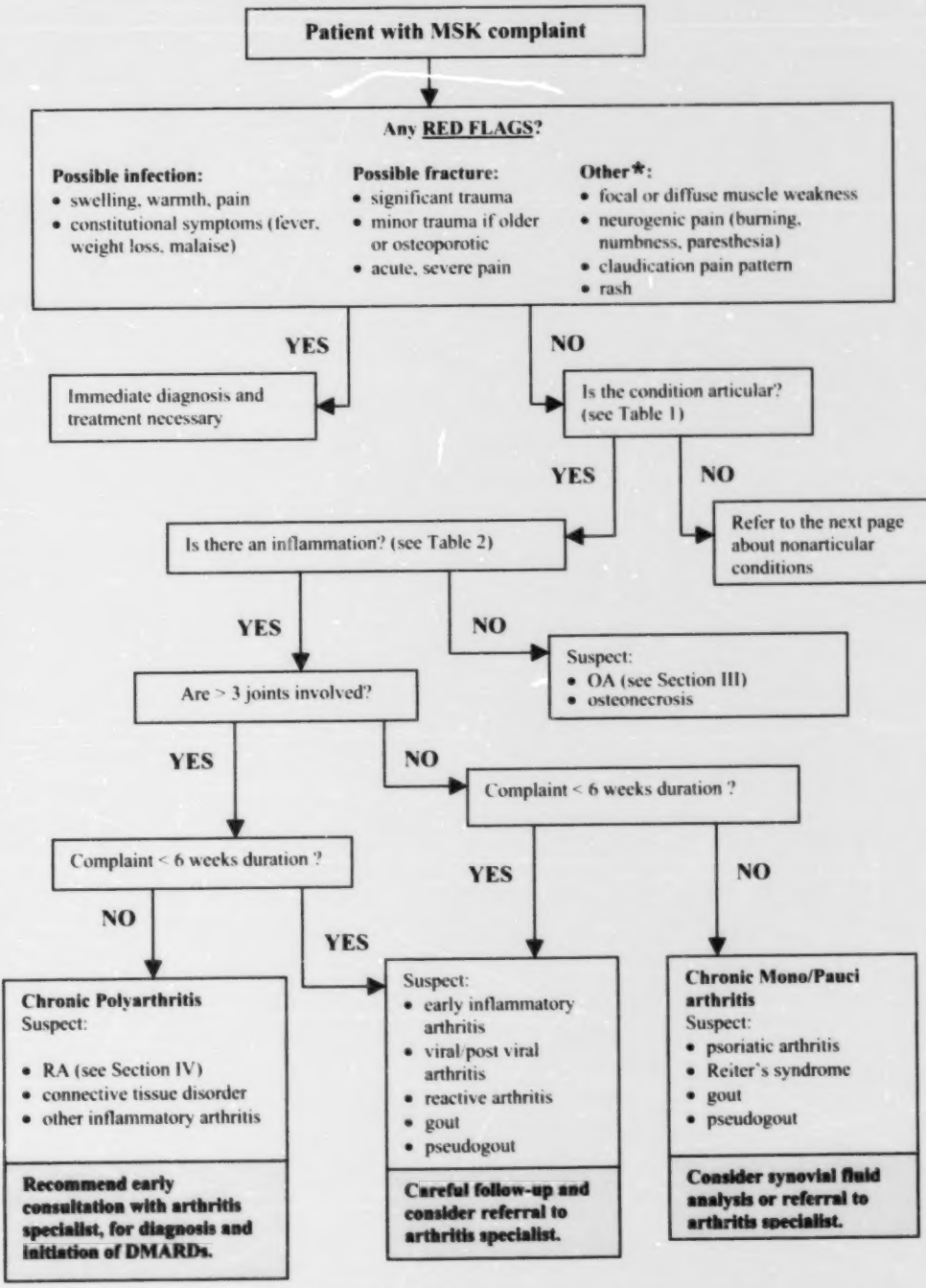
Ontario Treatment Guidelines for Osteoarthritis, Rheumatoid Arthritis, and Acute Musculoskeletal Injury

OPOT

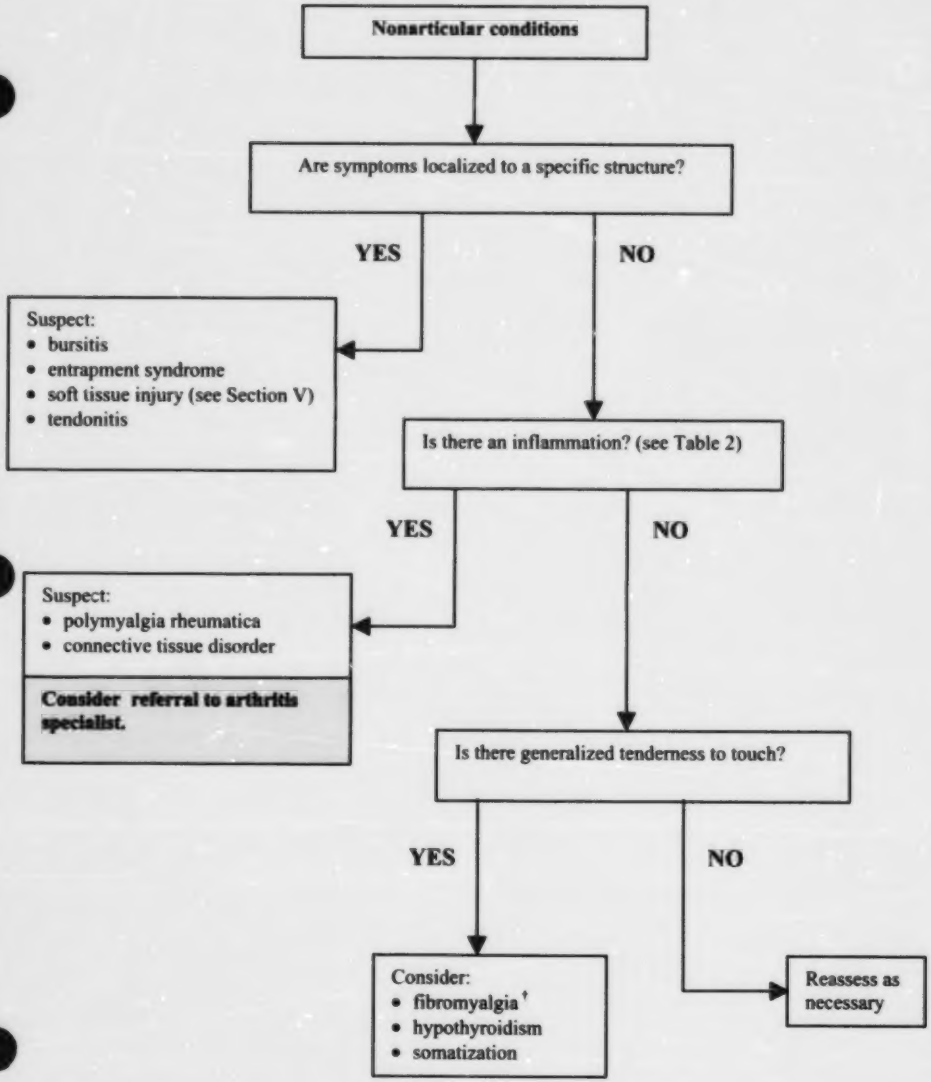
Ontario Program for Optimal Therapeutics

Guide to the Guidelines

Algorithm for the Initial Assessment of MSK Complaints (Adapted from <11>)



* Infers endocrinopathy, malignancy or metabolic disorder



† Fibromyalgia: widespread pain of > 3 months duration, pain on digital palpation (4kg of force) at ≥ 11 of 18 tender point sites, not covered by another diagnosis. <12>

Ontario Treatment Guidelines for Osteoarthritis, Rheumatoid Arthritis, and Acute Musculoskeletal Injury

Ontario Musculoskeletal Therapeutics Review Panel

June, 2000

For additional copies please write or call:

PUBLICATIONS ONTARIO
50 Grosvenor St.
Toronto, Ontario M7A 1N8
Telephone: (416)-326-5300 or toll-free in Ontario 1-800-668-9938.
Hearing impaired call: (416)-965-5130 or toll-free in Ontario 1-800-268-7095
Fax: (416)-326-5317

MasterCard and Visa accepted. Cheques and money orders payable to the Minister of Finance. Prepayments required.

ISBN 1-894706-00-5

Citation: Holbrook AM (Chair) for Ontario Musculoskeletal Therapy Review Panel. Ontario Treatment Guidelines for Osteoarthritis, Rheumatoid Arthritis, and Acute Musculoskeletal Injury. Toronto. Queen's Printer of Ontario, 2000.

Acknowledgment: Support for the development, production and distribution of this guideline was provided by the Ontario Program for Optimal Therapeutics (OPOT), made possible through a grant from the Ontario Ministry of Health and Long-Term Care.

DISCLAIMERS -- PLEASE READ CAREFULLY: This publication is designed for use by qualified health practitioners in providing health services, and is made available upon the express understanding that the authors, publisher, and other parties involved in its preparation are not providing medical or other professional advice to the general public. If required, such advice should be sought from a qualified health practitioner. This publication is not intended to replace other prescribing information, or as a substitute for the knowledge of a qualified health care provider. Nor can the guidelines take into account the unique needs of each patient or the variations in clinical resources available to a particular community or health care professional. Physicians are urged to consult drug information available in the medical literature, and from the manufacturer and other sources before prescribing.

This publication is based on information from sources believed to be reliable. While great effort has been taken to assure the completeness and accuracy of the information, it is not intended to reprint all of the information available on the subject of the publication, but rather to compile, complement and supplement other available sources. The Review Panel, publisher, printer and others contributing to the preparation of this document cannot accept liability for errors, omissions or any consequences arising from the use of the information.

Inclusion of a pharmaceutical product in these guidelines was determined solely on the basis of the Review Panel's expert professional assessment of the available evidence. It is not intended, and cannot be taken, as a recommendation that the product be included in the reimbursement policies of any drug plan or benefits manager.

Stakeholder groups were invited to participate in the development of these guidelines by reviewing and commenting upon the guidelines in draft form. These included health care professionals, professional societies, the pharmaceutical industry and the Ontario Ministry of Health and Long-Term Care.

Comments: A form is provided at the end of the document for the submission of reader's suggestions.

© 2000 Queen's Printer of Ontario

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the publisher.

TABLE OF CONTENTS

Section I: Introduction 2
1.1 Purpose and Organization of Guideline 2
1.2 Costs 2
1.3 Guideline Development Process 3
1.4 Use of Guideline 3
1.5 Grades of Recommendations 3
Section II: Evaluating Patients with Musculoskeletal Complaints 5
Figure 1. Algorithm for the Initial Assessment of MSK Complaints 8
Table 1: Articular vs. Nonarticular Disorders 10
Table 2: Inflammatory vs. Non-inflammatory Disorders 11
Section III: Osteoarthritis 13
3.1 Overview 14
3.1.1 Epidemiology 14
3.1.2 Pathophysiology 14
3.1.3 Clinical Presentation 15
3.2 Treatment of Osteoarthritis 15
3.2.1 Nonpharmacologic Therapy 15
3.2.2 Pharmacologic Therapy 16
3.2.3. Other Therapies 19
Table 3: Drug Therapy for Osteoarthritis 21
Table 4: Commonly Used NSAIDs 23
3.3 Osteoarthritis Bottom Lines 24
Section IV: Rheumatoid Arthritis 25
4.1 Overview 26
4.1.1 Epidemiology 26
4.1.2 Pathophysiology 26
4.1.3 Clinical Presentation 26
Table 5: 1987 Revised ARA Criteria for Diagnosis of RA 27
4.1.4 Assessment 27
4.2 Treatment of Rheumatoid Arthritis 28
4.2.1 Nonpharmacologic Therapy 28
4.2.2 Pharmacologic Therapy 28
Table 6: Drug Therapy for Rheumatoid Arthritis 30
Table 7: Commonly Used DMARDs 31
Table 8: Adverse Effects and Suggested Monitoring of DMARDs 32
4.3 Rheumatoid Arthritis Bottom Lines 33
Section V: Acute Soft Tissue Disorders 35
5.1 Overview 36
5.2 Treatment of Acute Soft Tissue Disorders 36
5.2.1 Nonpharmacologic Therapy 36
5.2.2 Pharmacologic Therapy 37
Table 9: Drug Therapy for Acute Soft Tissue Disorders 38
5.3 Acute Soft Tissue Disorders Bottom Lines 39
Section VI: Acute Low Back Pain 41
6.1 Overview 42
6.2 Management of Acute Low Back Pain 42
Figure 2: Algorithm for Management of Acute Low Back Pain 43
6.2.1 Non-pharmacologic Therapy 44
6.2.2 Pharmacologic Therapy 44
Table 10: Drug Therapy for Acute Low Back Pain 46
6.3 Acute Low Back Pain Bottom Lines 47
Appendix A 49
Core Review Panel Members 51
Members of Consensus Panel 52
External Peer Reviewers Who Provided Feedback Regarding Document 52
Appendix B 54
The Arthritis Society: Contact Information 54
Reference List 55
Comment Form 69

Section I

Introduction

SECTION I: INTRODUCTION

1.1 Purpose and Organization of Guideline

This guideline was commissioned and funded by the Ontario Program for Optimal Therapeutics (OPOT). OPOT is an independent agency established with a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The Ministry participated in guideline development only as one of the stakeholder groups asked to review and comment upon the guideline in draft form (along with health care professionals, professional societies, the pharmaceutical industry and others). OPOT's mandate is to provide Ontario health professionals with evidence-based recommendations for the cost-effective treatment of various conditions. A second component of OPOT's mandate is to develop methods of incorporating these guidelines into practice.

The following guidelines are directed towards the medical management of patients with musculoskeletal (MSK) disorders presenting to family physicians. These disorders are the most frequently reported cause of impairment affecting the adult population in Canada and the United States.<1-3> The 1990 Ontario Health Survey reported that diseases affecting the MSK system were reported by 22% of adults.<1> The prevalence of MSK disorders increases as age increases and is higher in women.<1> It has been estimated that one in seven patient visits to a family physician is prompted by MSK pain or dysfunction.<4> Of all chronic conditions, MSK disorders are the second most common reason for taking prescription or non-prescription medicines.<1>

The recommendations contained in this document focus on the drug treatment of four major MSK conditions: osteoarthritis (OA), rheumatoid arthritis (RA), acute low back pain and acute soft tissue disorders, namely sprains and strains. An algorithm is provided in Section II to assist with the initial assessment of patients with MSK signs and symptoms.

Tables are provided which summarize the recommended therapies. Primary tables summarize recommendations for each of the conditions, while secondary supportive tables list specific agents that can be used. In the primary tables, first-line agents are listed first, while second-line agents and other therapies are listed thereafter. Medications are designated as **"first-line"** solely based on the strength of efficacy and adverse effect data, availability, cost and convenience and not on the basis of reimbursement policies. The column in the tables titled "Evidence" lists the randomized controlled trials (RCTs) and systematic reviews that support the inclusion of the particular agent or class.

1.2 Costs

All costs were calculated using the Ontario Drug Benefit (ODB) formulary costs for the lowest priced interchangeable product. In cases where no ODB data were available, cost were obtained from the manufacturer. Retail costs for over-the-counter (OTC) drugs (e.g. ibuprofen) were obtained from a survey of five community pharmacies across Ontario. Pharmacies across Ontario add a professional fee (e.g., $6.47 for ODB reimbursement) to each prescription upon purchase by a consumer. Professional fees are not included in costs listed in the tables since they vary according to reimbursement status of the consumer.

1.3 Guideline Development Process

The document was developed using the following methodology. A thorough literature search was undertaken using the following databases: MEDLINE, EMBASE, and The Cochrane Database of Systematic Reviews (CDSR). Relevant randomized clinical trials, meta-analyses, practice guidelines, and economic analyses were identified and retrieved. Each recommendation was assigned based on the quality of the evidence (Section 1.5).

A draft document was developed in the Centre for Evaluation of Medicines based on the extensive literature review and recent practice guidelines.<4-7> A review panel was formed consisting of family physicians, rheumatologists, clinical pharmacologists, physiatrists, pharmacists, epidemiologists and a consumer representative representing each region of the province as well as academic and community practice. This group reviewed the first draft document individually, then met to provide consensus and additional evidence. The resultant second draft was then mailed to a larger consensus panel, which consisted of the review panel plus additional representatives of the disciplines listed above. A second meeting was held to further discuss modification of the document. As a result of these deliberations, a third draft was formulated for "stakeholder review". Stakeholders included more than 100 representatives of all relevant professional societies, government branches, pharmaceutical companies, consumers, plus additional experts and practicing clinicians. Their comments were collated and assessed by reviewers blinded to the source of the comment. Those accepted were incorporated into a final draft, which, once approved by the review panel, was readied for publication.

1.4 Use of Guidelines

These guidelines are intended to assist clinicians, primarily family physicians, with caring for adults who are suffering from MSK disorders. They cannot be relied upon for advice for children or pregnant women.

1.5 Grades of Recommendations

Information on the management of patients with MSK disorders is incomplete. There are numerous pharmacologic and nonpharmacologic therapies for MSK conditions. Unfortunately, there is also a lack of good quality comparative studies that clearly establish superiority of one agent over another. These guidelines provide recommendations based on the best available evidence. The following grades were used to indicate the quantity and quality of evidence supporting each recommendation: <8>

Grade A: from well-designed, randomized controlled trials or meta-analyses with consistent results that demonstrate a clinically important benefit.

Grade B: from well-designed, randomized controlled trials or meta-analyses with inconsistent results or demonstrating equivocal benefit.

Grade C: from non-randomized trials, concurrent cohort (contemporaneous controls followed similarly) and case-control studies.

Grade D: from before and after studies, case series, expert opinion, or consensus.

Section II

Evaluating Patients with Musculoskeletal Complaints

SECTION II: EVALUATING PATIENTS WITH MUSCULOSKELETAL COMPLAINTS

(see Figure 1)

When patients present to a family physician with MSK complaints, it is important to first rule out conditions that require immediate care. These conditions or "red flags" include<4>:

- history of significant trauma
- hot and swollen joint
- acute severe pain
- significant constitutional signs and symptoms (e.g., fever, weight loss, and malaise)
- focal or diffuse muscle weakness
- neurogenic pain (e.g., burning, numbness, and paresthesia)
- claudication pain pattern

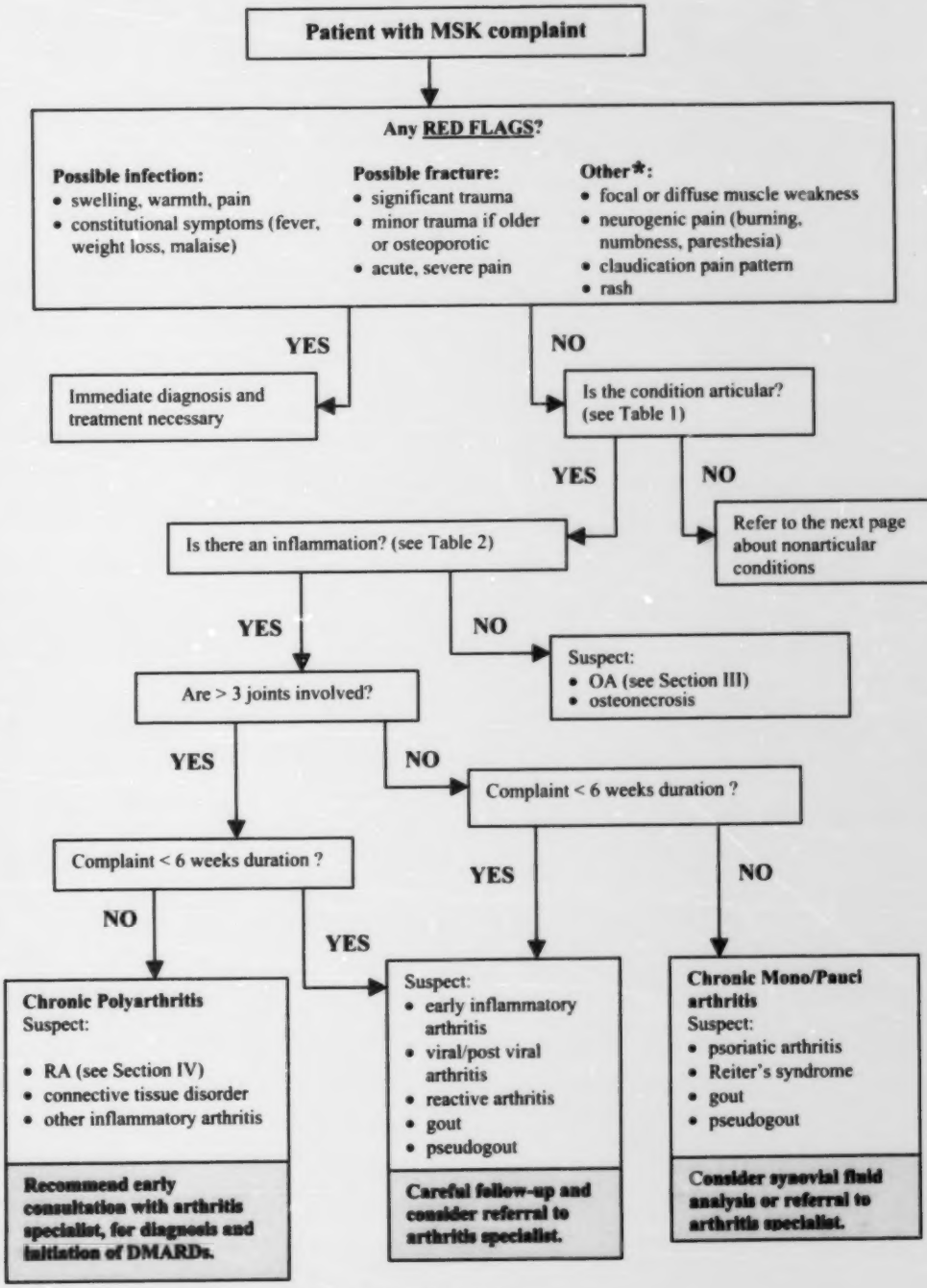
Relevant questions when diagnosing MSK complaints include:

- Is the condition articular vs. non-articular? (see Table 1)
- Is the condition inflammatory vs. non-inflammatory? (see Table 2)
- If the condition is articular, is it pauci-articular (≤ 3 joints) or poly-articular (> 3 joints)?
- Is the condition acute (< 6 weeks) or chronic (≥ 6 weeks)?

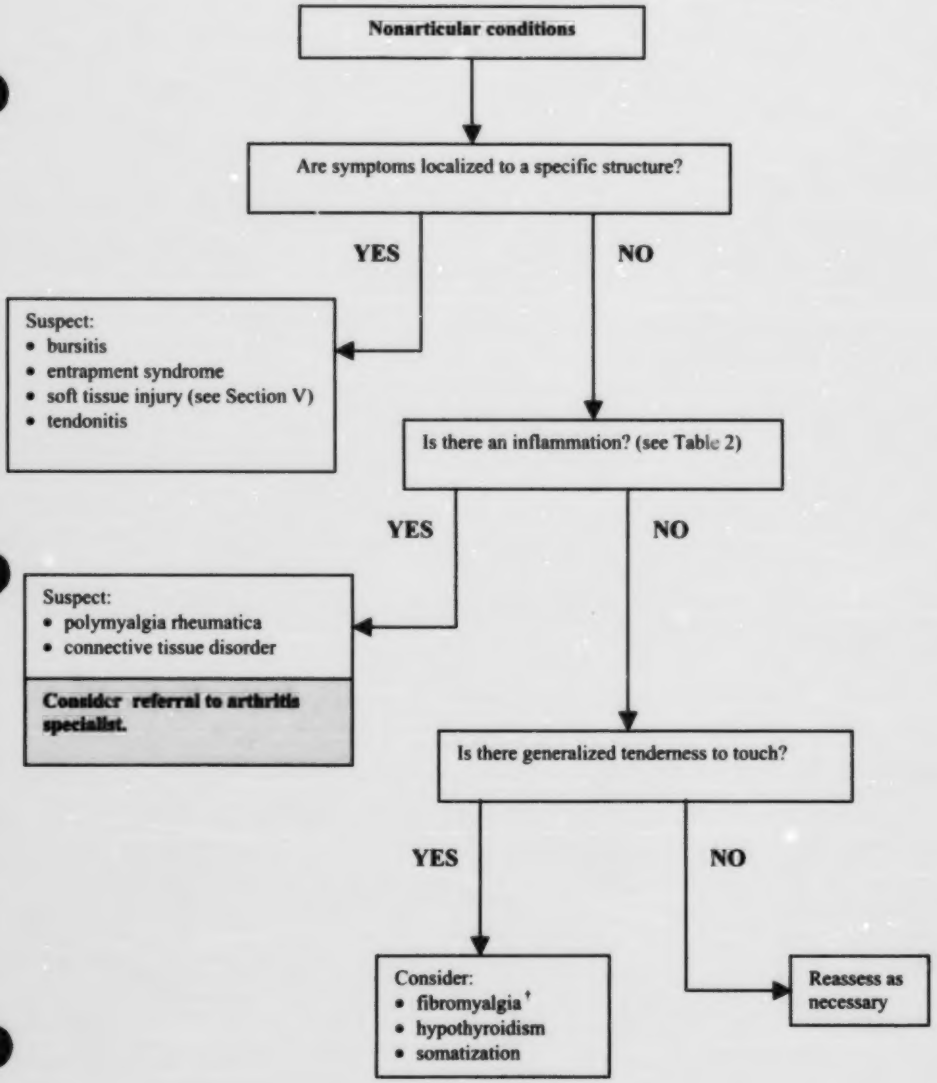
Laboratory tests can be helpful in evaluating MSK disorders, however they often lack specific diagnostic power. Acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are non-specific. Rheumatoid factor (RF) testing is of limited usefulness due to high false-positive and false-negative results for RA therefore should be limited to cases with a high suspicion of rheumatoid arthritis. High antinuclear antibody (ANA) titres may suggest connective tissue disorders, however the prevalence of elevated ANA titres increases with age to 5-25% in persons >40 years old. Lyme disease serologies are not clinically useful in patients who only have nonspecific symptoms of myalgia, headache, fatigue or arthralgia.<9,10> Synovial fluid analysis is useful in evaluating patients with suspected crystal or infective arthropathies. For evaluating articular disease, plain x-rays remain the best imaging modality, when attempting to confirm or rule out a clinical diagnosis.<11>

All patients in whom RA is suspected should proceed to further assessment and management. This is to ensure that therapy with disease-modifying anti-rheumatic drugs (DMARDs) is considered early. (see section 4.2) In addition, patients with other inflammatory arthritides should be considered for referral to an arthritis specialist.

Figure 1. Algorithm for the Initial Assessment of MSK Complaints (Adapted from <11>



* Infers endocrinopathy, malignancy or metabolic disorder



† Fibromyalgia: widespread pain of > 3 months duration, pain on digital palpation (4kg of force) at ≥ 11 of 18 tender point sites, not covered by another diagnosis. <12>

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

micromedia
a division of IHS Canada

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

Table 1: Articular vs. Nonarticular Disorders Adapted from <11>

	Characteristics of Condition	
Feature	**Articular**	**Nonarticular**
Anatomic Structures	• juxta-articular bone • articular cartilage • intra-articular ligaments • menisci (knee) • synovial fluid • synovium • joint capsule	• tendons • bursae • extra-articular ligament • muscle • fascia • bone • nerve • skin
Symptoms and Signs		
Pain or Tenderness	• localized to joint • deep and poorly localized • specific referral patterns	• localized to extra-articular structures • 'point' tenderness, superficial
Pain on Movement	• with active and passive movement • with movement in many planes • localized to joint	• with active movement • with movement in specific planes • rarely localized to joint
Swelling	• common, related to articular structures • include: synovial effusion, synovial thickening, bony enlargement	• may be present • not limited to articular structures
Limitation of Movement	• frequent on both passive and active range of movements • related to mechanical derangement or joint pain	• may be present but usually limited to active range of movement • related to extra-articular mechanical abnormality, diffuse pain or weakness
Crepitation	• may be present	• absent/unrelated
Instability	• may be present	• absent/unrelated
Locking of Joint	• may be present	• absent/unrelated
Deformity	• may be present	• rare, except with antecedent trauma • associated with extra-articular abnormality
Radiographic Changes	• common in chronic conditions • uncommon in acute conditions except trauma	• uncommon/unrelated • soft tissue calcification

Table 2: Inflammatory vs. Non-inflammatory Disorders Adapted from <11>

	Characteristics of Condition	
Feature	**Inflammatory**	**Non-inflammatory**
A. Clinical Features		
Joint pain	yes (with activity and rest)	yes (with activity)
Joint swelling	soft tissue	bony (if present)
Local erythema	sometimes	absent
Local warmth	sometimes	absent
Morning stiffness	prolonged (> 60 minutes)	variable (< 60 minutes)
Systemic symptoms	common	rare
B. Optional Investigations		
ESR, CRP	increase	normal for age
Hemoglobin	normal or low	normal
Serum albumin	normal or low	normal
Synovial fluid WBC/mm^3	≥ 2000	< 2000
Synovial fluid % PMN	≥ 75%	< 75%

ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, WBC = white blood cell, PMN = polymorphonucleocytes

Table 1: Articular vs. Nonarticular Disorders Adapted from <11>

	Characteristics of Condition	
Feature	**Articular**	**Nonarticular**
Anatomic Structures	• juxta-articular bone • articular cartilage • intra-articular ligaments • menisci (knee) • synovial fluid • synovium • joint capsule	• tendons • bursae • extra-articular ligament • muscle • fascia • bone • nerve • skin
Symptoms and Signs		
Pain or Tenderness	• localized to joint • deep and poorly localized • specific referral patterns	• localized to extra-articular structures • 'point' tenderness, superficial
Pain on Movement	• with active and passive movement • with movement in many planes • localized to joint	• with active movement • with movement in specific planes • rarely localized to joint
Swelling	• common, related to articular structures • include: synovial effusion, synovial thickening, bony enlargement	• may be present • not limited to articular structures
Limitation of Movement	• frequent on both passive and active range of movements • related to mechanical derangement or joint pain	• may be present but usually limited to active range of movement • related to extra-articular mechanical abnormality, diffuse pain or weakness
Crepitation	• may be present	• absent/unrelated
Instability	• may be present	• absent/unrelated
Locking of Joint	• may be present	• absent/unrelated
Deformity	• may be present	• rare, except with antecedent trauma • associated with extra-articular abnormality
Radiographic Changes	• common in chronic conditions • uncommon in acute conditions except trauma	• uncommon/unrelated • soft tissue calcification

Table 2: Inflammatory vs. Non-inflammatory Disorders Adapted from <11>

	Characteristics of Condition	
Feature	**Inflammatory**	**Non-inflammatory**
A. Clinical Features		
Joint pain	yes (with activity and rest)	yes (with activity)
Joint swelling	soft tissue	bony (if present)
Local erythema	sometimes	absent
Local warmth	sometimes	absent
Morning stiffness	prolonged (> 60 minutes)	variable (< 60 minutes)
Systemic symptoms	common	rare
B. Optional Investigations		
ESR, CRP	increase	normal for age
Hemoglobin	normal or low	normal
Serum albumin	normal or low	normal
Synovial fluid WBC/mm^3	≥ 2000	< 2000
Synovial fluid % PMN	≥ 75%	< 75%

ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, WBC = white blood cell, PMN = polymorphonucleocytes

Section III

Osteoarthritis

SECTION III: OSTEOARTHRITIS

3.1 Overview

Osteoarthritis (OA) is the most common form of arthritis in Ontario.<13>It is a slowly progressive monoarticular (or less commonly polyarticular) disorder of unknown cause and obscure pathogenesis.<13> It most often involves the distal joints of the hands and feet, the spine and weight-bearing joints such as the knees and hips. <13> Patients with OA most often present with pain in and around the affected joint that is usually worse with weight bearing and improved with rest.<5,6,14> They often report morning stiffness and gelling phenomenon (stiffness after inactivity/rest). On physical examination, the joints are usually tender to palpation, may have bony enlargement, crepitus with motion, and/or limitation of motion. <5,6> Unlike rheumatoid arthritis (RA), signs of inflammation are usually absent or very mild.

Osteoarthritis surpasses cardiovascular disease as a cause of long-term disability. <1> The costs associated with the ongoing care of these patients in terms of medications, days lost from work, and the cost of long-term care facilities, are high.<13>

There is no known cure for OA. Therefore, the goals of therapy are to reduce pain, maintain or improve joint mobility, limit functional disability and educate the patient and family about the disease and its therapy. <5> These goals are best achieved with the use of a multidisciplinary approach involving family physicians, specialists such as internists, rheumatologists, physiatrists and orthopedic surgeons, plus physiotherapists, occupational therapists and pharmacists.

3.1.1 Epidemiology

Estimates of OA prevalence vary depending on the factors included in the definition. <3,14> Generally, OA is thought to affect more than 10-12% of the population.<3,13> Prevalence is relatively low below the age of 50, but rises precipitously with advancing age. Almost all persons >65 years old show signs of OA based on radiographic criteria but only 33% of the same group will have symptomatic OA.<3,13> Although males and females are equally likely to develop OA of the hip, OA of the knees and hands is more common in older women than men.<3>

3.1.2 Pathophysiology

The disease primarily affects the cartilage, often with progressive changes. <5,6> Two primary factors lead to joint failure:

- progressive breakdown of articular cartilage that lines joint surfaces and
- dense, smooth surface bone formation at the base of the cartilage lesion and the formation of osteophytes at the joint margins.

This process is different than the "wear and tear" that occurs with aging. The condition is characterized by focal erosive lesions, cartilage destruction, subchondral sclerosis, cyst formation, and large osteophytes at the margins of the joint. <13> No single factor appears to cause OA. Several factors probably contribute to the process, including biochemical, biomechanical, inflammatory, and immunologic factors.

3.1.3 Clinical Presentation

Clinically, OA is characterized by pain, deformity, enlargement of joints and limitation of motion.<13> The disease, however, presents itself differently in different joints.<14,15> In contrast to RA, OA presents as asymmetrical joint involvement and affects the larger joints such as the hips, knees, cervical and lumbar spine, the metatarsophalangeal (MTP) joint of the toe, and the distal interphalangeal (DIP), proximal interphalangeal (PIP) and carpal metacarpal (CMC) joints of the hands. The stiffness observed in OA usually lasts less than 30-60 minutes, depending on the joint involved. No specific laboratory abnormalities occur in OA. The rheumatoid factor is negative. Contrary to RA, systemic abnormalities have not been detected. <14,15>

Radiologic changes seen on plain films are highly characteristic of the disease. Additional radiologic techniques are rarely required to confirm the diagnosis. There is no consistent relationship found between the degree of radiologic changes present and the degree of symptoms reported.<14,15>

3.2 Treatment of Osteoarthritis

3.2.1 Nonpharmacologic Therapy

Although these guidelines are designed to focus on drug therapy, nonpharmacologic treatments for OA are important. Nonpharmacologic interventions supported by evidence include: exercise<16-18>, exercise plus physiotherapy<19>, patient education for self-management<20,21> and social support<22-24>. There is a paucity of data on weight loss as a treatment for OA in the obese. There are sparse or inconsistent data to support the use of other nonpharmacologic treatments such as transcutaneous electrical nerve stimulation (TENS), acupuncture, low-energy laser or ultrasound.<16,25>

Exercise reduces pain and improves functioning in OA of the knee.<16,17> Programs that have been evaluated include stretching and quadriceps strengthening, aerobic exercise (walking or swimming) and resistance exercise. Attendance in programs such as an arthritis self-management program can decrease pain, decrease frequency of physician visits, and provide an overall improvement in quality of life.<20,21> More information about these programs can be obtained by contacting The Arthritis Society (see Appendix B). The provision of social support in the form of monthly telephone follow-up with OA patients can improve pain and functional status.<22-24>

Occupational therapists and physiotherapists may be helpful in OA management as they can implement exercise programs for patients with OA with the aim to decrease their pain and improve their function.<16,26,27> Canes and other devices (e.g., raised toilet seat, dressing sticks for socks, and wall bars in bathroom) may assist in performance of activities of daily living (ADLs).<5,6>

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

micromedia
a division of IHS Canada

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

3.2.2 Pharmacologic Therapy

Since no medications are proven to reverse the damage caused by OA, the primary indication for medical therapy is for analgesia.<5,6> The agent of first choice for this indication is **acetaminophen** at full doses (i.e., maximum 1000 mg four times daily).

Three randomized controlled trials (RCTs) suggest that acetaminophen is comparable to nonsteroidal anti-inflammatory drug (NSAID) therapy for mild to moderate OA of the knee.<28>,<29>, <30> Because of superior safety and lower cost, acetaminophen is the first-line therapy in OA.

This is a Grade B recommendation.

Are there any risks with acetaminophen?

Acetaminophen's main risk is in overdose, usually single doses > 10 grams, where hepatotoxicity can occur. <31> The maximum dose of acetaminophen may be lower in patients with serious liver or kidney disease. High doses of acetaminophen may potentiate warfarin effect, necessitating closer scrutiny of INR values. Both ethanol in high doses and phenytoin have been implicated as potentiating acetaminophen-associated hepatotoxicity. <32>

What are the gastrointestinal (GI) side effects of NSAIDs and how often do they occur?

NSAIDs produce a variety of GI toxicities from relatively minor side effects such as nausea and dyspepsia to more serious GI events such as hemorrhage, perforation and death.<33-35> Nausea and dyspepsia are relatively common side effects, occurring in 10-25% of patients, and correlate poorly with serious GI events.<36> Hemorrhage, perforation, and death associated with NSAID use are more rare, occurring at a cumulative rate of 0.7 to 1.3% per year. In Ontario, 0.7% of new NSAID users over the age of 65 years experienced a GI bleed requiring hospitalization in 1995.<37> Prospective data from a large, systematic post-marketing surveillance program of patients with arthritis estimates that the mortality rate attributable to NSAID use is 0.22% per year, about four times the risk of non-NSAID consumers. <36> Although the yearly incidence figures are low, utilization of NSAIDs is high resulting in significant total numbers of serious GI events due to NSAIDs.

Who is at greatest risk for serious GI events with NSAID use?

Patients who are considered high risk for serious GI events have the following risk factors: age > 65 years, history of peptic ulcer disease, history of GI bleeding or cardiovascular disease. Patients with rheumatoid arthritis with one risk factor have approximately 1% risk of having serious GI adverse event (perforation, ulcer and bleeding), in 6 months. With all four risk factors present, this risk increases to 9% in 6 months. <38> The risk in other NSAID-using populations is likely lower but has not been clarified.<39> nor has risk over time beyond 6 months. RCTs have failed to find a significant increase in serious GI events when corticosteroids are taken with NSAIDs.<38,40> High risk patients should avoid NSAID use. If NSAID use cannot be avoided, high risk patients should receive prophylaxis against serious GI events with either misoprostol<38,41-43> or a proton pump inhibitor (PPI) <43-47> or a switch to a

3.2.2 Pharmacologic Therapy

Since no medications are proven to reverse the damage caused by OA, the primary indication for medical therapy is for analgesia.<5,6> The agent of first choice for this indication is **acetaminophen** at full doses (i.e., maximum 1000 mg four times daily).

Three randomized controlled trials (RCTs) suggest that acetaminophen is comparable to nonsteroidal anti-inflammatory drug (NSAID) therapy for mild to moderate OA of the knee.<28>,<29>, <30> Because of superior safety and lower cost, acetaminophen is the first-line therapy in OA.

This is a Grade B recommendation.

Are there any risks with acetaminophen?

Acetaminophen's main risk is in overdose, usually single doses > 10 grams, where hepatotoxicity can occur. <31> The maximum dose of acetaminophen may be lower in patients with serious liver or kidney disease. High doses of acetaminophen may potentiate warfarin effect, necessitating closer scrutiny of INR values. Both ethanol in high doses and phenytoin have been implicated as potentiating acetaminophen-associated hepatotoxicity. <32>

What are the gastrointestinal (GI) side effects of NSAIDs and how often do they occur?

NSAIDs produce a variety of GI toxicities from relatively minor side effects such as nausea and dyspepsia to more serious GI events such as hemorrhage, perforation and death.<33-35> Nausea and dyspepsia are relatively common side effects, occurring in 10-25% of patients, and correlate poorly with serious GI events.<36> Hemorrhage, perforation, and death associated with NSAID use are more rare, occurring at a cumulative rate of 0.7 to 1.3% per year. In Ontario, 0.7% of new NSAID users over the age of 65 years experienced a GI bleed requiring hospitalization in 1995.<37> Prospective data from a large, systematic post-marketing surveillance program of patients with arthritis estimates that the mortality rate attributable to NSAID use is 0.22% per year, about four times the risk of non-NSAID consumers. <36> Although the yearly incidence figures are low, utilization of NSAIDs is high resulting in significant total numbers of serious GI events due to NSAIDs.

Who is at greatest risk for serious GI events with NSAID use?

Patients who are considered high risk for serious GI events have the following risk factors: age > 65 years, history of peptic ulcer disease, history of GI bleeding or cardiovascular disease. Patients with rheumatoid arthritis with one risk factor have approximately 1% risk of having serious GI adverse event (perforation, ulcer and bleeding), in 6 months. With all four risk factors present, this risk increases to 9% in 6 months. <38> The risk in other NSAID-using populations is likely lower but has not been clarified.<39> nor has risk over time beyond 6 months. RCTs have failed to find a significant increase in serious GI events when corticosteroids are taken with NSAIDs.<38,40> High risk patients should avoid NSAID use. If NSAID use cannot be avoided, high risk patients should receive prophylaxis against serious GI events with either misoprostol<38,41-43> or a proton pump inhibitor (PPI) <43-47> or a switch to a

+6 -1

COX-2 inhibiting NSAID considered (*see further below*). As prophylactic agents for serious GI events, H_2 receptor antagonists are less effective than misoprostol or PPIs.<48-50> Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>

Are some NSAIDs safer than others?

All NSAIDs have been found to cause the full spectrum of GI toxicities. Several authors have attempted to compare the relative risks of serious GI complications with individual NSAIDs using case-control or cohort data.<52-56> Interpreting these studies is difficult due to many potential confounders, such as non-randomized design, non-equivalent dose comparisons, patient's disease severity and comorbid illness. Accepting these flaws, some patterns have been found: low dose ibuprofen appears to be the least toxic, diclofenac and naproxen intermediate, and piroxicam, ketoprofen and tolmetin appear to be the most toxic. However, ibuprofen at high doses (>1500mg/day) carries a similar risk to other NSAIDs at therapeutically equivalent doses.<53,54>. It is possible that all of the apparent differences in risk between NSAIDs are the result of dose unequivalence and the lack of large head-to-head randomized trials.
There is no convincing evidence that sustained release (SR) or enteric-coated (EC) formulations of NSAIDs have lower rates of symptomatic NSAID-induced gastropathy when compared to immediate release formulations.<57-67> Comparable efficacy has been demonstrated between the formulations in patients with OA and RA.<57-67>

The only pre-manufactured topical NSAID available in Canada is salicylate. A summary of trials on all topical NSAIDs suggests modest benefit in acute and chronic musculoskeletal conditions. <68-70> Since both the systemic absorption of the products is low as well as the apparent risk of GI bleeding, it is likely that topical NSAIDs are similar to low dose oral NSAIDs. <67> The main problems with topical products are difficulty controlling dose and the potential for salicylate poisoning. <71-75>

What is the role for selective COX-2 inhibiting NSAIDs?

NSAIDs that selectively inhibit the type 2 isoform of cyclo-oxygenase (COX-2) theoretically may treat inflammatory conditions with less effect on GI mucosal barriers.<76,77> Celecoxib and rofecoxib are available in Canada. Data available to date suggest that the efficacy of celecoxib 200 mg per day for osteoarthritis and celecoxib 400 mg per day for rheumatoid arthritis is equivalent to usual doses of older NSAIDs. <78-80> Studies of rofecoxib for the treatment of patients with OA, have suggested that doses of 12.5 and 25 mg per day have comparable efficacy to usual doses of older NSAIDs.<81>
Comparative trials of the COX-2 inhibiting NSAIDs versus acetaminophen for osteoarthritis are urgently needed to establish relative efficacy and safety.
Concerns regarding COX-2 NSAIDs delaying ulcer healing as well as causing renal and hepatic impairment remain unabated. The celecoxib product monograph lists sulpha allergy as a contraindication. The true cross-allergy rate is unknown.
If benefit of the COX-2 inhibitor agents is similar to other NSAIDs, then the niche for the COX-2 inhibiting NSAIDs will be determined by the relative frequency of serious GI events (ulcer, perforation and GI bleeding) and their cost. Early trial results of celecoxib and rofecoxib have suggested favourable impact on endoscopic end points.<79,82> However, there is increasing evidence that most endoscopic ulcers are unimportant clinically and that endoscopic ulcers are easier to prevent than clinically important GI events. <36,39,83> A recent pooled analysis of 8 randomized trials found that the

incidence of serious GI events in osteoarthritis patients on rofecoxib was 1.3% over 12 months compared to 1.8% for those receiving regular full dose NSAIDs.<83> This means that 200 such patients need to be treated with rofecoxib instead of usual NSAIDs for 1 year to prevent 1 serious GI event. Neither of the COX-2 NSAIDs have been studied in patients at high risk of serious GI events.
Celecoxib and rofecoxib are priced at the higher end of NSAID pricing ($1.25 - $2.50 per day). They are more expensive than the combination of many NSAIDs plus misoprostol but less expensive than NSAID plus PPI (e.g., pantoprazole, lansoprazole, omeprazole).
In summary, COX-2 selective NSAIDs such as celecoxib and rofecoxib are most appropriate for patients who require long term NSAID therapy and who are at high risk of serious GI events.

Based on evidence of similar efficacy and early evidence of somewhat lower rates of serious GI events, selective COX-2 inhibiting NSAIDs can be considered for patients at high risk of serious GI events.

This is a Grade B recommendation.

What is the role of Helicobacter pylori in NSAID-related gastropathy?

Testing for and eradicating *Helicobactor pylori* in patients with NSAID-related peptic ulcer disease is controversial at this point.<84-89> One well-designed RCT demonstrated a reduction in NSAID-related ulcer occurrence over 8 weeks when H. pylori was eradicated.<87> However, 2 RCTs evaluating acid suppression therapy and secondary prophylaxis of NSAID-associated ulcers found that the presence of H. Pylori was a positive predictor of healing and maintenance of remission.<43,47> In a third trial of patients requiring NSAIDs who had current or past ulcers or significant dyspepsia, eradication of H. pylori did not improve ulcer recurrence rates or dyspepsia.<89> Further study is necessary to clarify the role of *H. pylori* eradication in this setting.<84>

What other adverse effects are caused by NSAIDs?

Less commonly, NSAIDs are associated with renal insufficiency<90,91>, usually mild increases in supine blood pressure<92>, worsened congestive heart failure and rarely, hepatitis. Therefore, monitoring is important for chronic NSAID users. Baseline and follow-up laboratory evaluations include a complete blood count (CBC), serum creatinine, AST and ALT.<93> Patients should regularly be questioned about dark/black stool, dyspepsia, nausea/vomiting, abdominal pain, edema and shortness of breath.<93>

NSAIDs are superior to placebo for OA of the knee and hip, however serious GI toxicity limits their routine use (see above text).
NSAIDs may be used in patients with moderate to severe osteoarthritis and in those whose symptoms are not adequately controlled by acetaminophen.

This is a Grade B recommendation.

3.2.3. Other Therapies

Despite their widespread use, few studies have evaluated the efficacy and safety of **combination analgesics** (e.g. acetaminophen with codeine) in the treatment of chronic MSK pain. One RCT compared acetaminophen 3 g/d to acetaminophen plus 180 mg/d of codeine in the treatment of pain due to OA of the hip.<94> At the end of week 1, the combination was more effective in reducing pain, however by the 3 weeks there was little difference between the treatment groups. Adverse effects such as nausea, dizziness, vomiting and constipation occurred more often in the combination group, causing 36% of patients to drop out of study after 1 week.<94> Based on the available data, it is suggested that sustained-release opioid therapy may benefit selected patients with chronic musculoskeletal pain. <95> Data comparing combination analgesics and NSAIDs are lacking.

Combination analgesics may be used to provide additional short-term analgesia. Compared to acetaminophen alone they have more adverse effects.

This is a Grade D recommendation.

The use of **intra-articular corticosteroid injections** is appropriate for patients who have OA of the knee with an effusion and local signs of inflammation.<6> An acutely inflamed, painful knee may be aspirated and injected with a corticosteroid to reduce pain and increase quadriceps strength in the short-term.<96-99> Injections may be useful as monotherapy in certain patients or in combination with systemic therapy. Although not well supported by clinical data, intra-articular injections are generally not administered more than three to four times per year because of a theoretical concern about the development of progressive cartilage damage with repeated injection to weight-bearing joints.<6>

Intra-articular corticosteroid injections may provide acute pain relief but their effectiveness wanes after approximately 4-6 weeks.<96-99>

This is a Grade B recommendation.

Hyaluronan and its derivatives attempt to increase the viscoelasticity of synovial fluid in osteoarthritic joints. These joints have lower concentrations of endogenous hyaluronic acid, resulting in loss of lubrication and less protection from mechanical stress.<100> Several double blind RCTs have demonstrated modest pain relief compared to placebo, in patients with mild to moderate OA of the knee after 3 to 5 weeks of weekly intra-articular hyaluronan injections.<101-106> Beneficial effects lasted up to 6 months in one of the studies.<105> One trial suggested benefit when hyaluronans are added to NSAID therapy.<106> However, two double blind RCTs found no benefit for intra-articular hyaluronan therapy over placebo <107,108>There have been no direct comparisons of the different hyaluronan derivatives. The least expensive hyaluronan is over $200 per course (3 injections).

incidence of serious GI events in osteoarthritis patients on rofecoxib was 1.3% over 12 months compared to 1.8% for those receiving regular full dose NSAIDs.<83> This means that 200 such patients need to be treated with rofecoxib instead of usual NSAIDs for 1 year to prevent 1 serious GI event. Neither of the COX-2 NSAIDs have been studied in patients at high risk of serious GI events.
Celecoxib and rofecoxib are priced at the higher end of NSAID pricing ($1.25 - $2.50 per day). They are more expensive than the combination of many NSAIDs plus misoprostol but less expensive than NSAID plus PPI (e.g., pantoprazole, lansoprazole, omeprazole).
In summary, COX-2 selective NSAIDs such as celecoxib and rofecoxib are most appropriate for patients who require long term NSAID therapy and who are at high risk of serious GI events.

Based on evidence of similar efficacy and early evidence of somewhat lower rates of serious GI events, selective COX-2 inhibiting NSAIDs can be considered for patients at high risk of serious GI events.

This is a Grade B recommendation.

What is the role of Helicobacter pylori in NSAID-related gastropathy?

Testing for and eradicating *Helicobactor pylori* in patients with NSAID-related peptic ulcer disease is controversial at this point.<84-89> One well-designed RCT demonstrated a reduction in NSAID-related ulcer occurrence over 8 weeks when H. pylori was eradicated.<87> However, 2 RCTs evaluating acid suppression therapy and secondary prophylaxis of NSAID-associated ulcers found that the presence of H. Pylori was a positive predictor of healing and maintenance of remission.<43,47> In a third trial of patients requiring NSAIDs who had current or past ulcers or significant dyspepsia, eradication of H. pylori did not improve ulcer recurrence rates or dyspepsia.<89> Further study is necessary to clarify the role of *H. pylori* eradication in this setting.<84>

What other adverse effects are caused by NSAIDs?

Less commonly, NSAIDs are associated with renal insufficiency<90,91>, usually mild increases in supine blood pressure<92>, worsened congestive heart failure and rarely, hepatitis. Therefore, monitoring is important for chronic NSAID users. Baseline and follow-up laboratory evaluations include a complete blood count (CBC), serum creatinine, AST and ALT.<93> Patients should regularly be questioned about dark/black stool, dyspepsia, nausea/vomiting, abdominal pain, edema and shortness of breath.<93>

NSAIDs are superior to placebo for OA of the knee and hip, however serious GI toxicity limits their routine use (see above text).
NSAIDs may be used in patients with moderate to severe osteoarthritis and in those whose symptoms are not adequately controlled by acetaminophen.

This is a Grade B recommendation.

3.2.3. Other Therapies

Despite their widespread use, few studies have evaluated the efficacy and safety of **combination analgesics** (e.g. acetaminophen with codeine) in the treatment of chronic MSK pain. One RCT compared acetaminophen 3 g/d to acetaminophen plus 180 mg/d of codeine in the treatment of pain due to OA of the hip.<94> At the end of week 1, the combination was more effective in reducing pain, however by the 3 weeks there was little difference between the treatment groups. Adverse effects such as nausea, dizziness, vomiting and constipation occurred more often in the combination group, causing 36% of patients to drop out of study after 1 week.<94> Based on the available data, it is suggested that sustained-release opioid therapy may benefit selected patients with chronic musculoskeletal pain. <95> Data comparing combination analgesics and NSAIDs are lacking.

Combination analgesics may be used to provide additional short-term analgesia. Compared to acetaminophen alone they have more adverse effects.

This is a Grade D recommendation.

The use of **intra-articular corticosteroid injections** is appropriate for patients who have OA of the knee with an effusion and local signs of inflammation.<6> An acutely inflamed, painful knee may be aspirated and injected with a corticosteroid to reduce pain and increase quadriceps strength in the short-term.<96-99> Injections may be useful as monotherapy in certain patients or in combination with systemic therapy. Although not well supported by clinical data, intra-articular injections are generally not administered more than three to four times per year because of a theoretical concern about the development of progressive cartilage damage with repeated injection to weight-bearing joints.<6>

Intra-articular corticosteroid injections may provide acute pain relief but their effectiveness wanes after approximately 4-6 weeks.<96-99>

This is a Grade B recommendation.

Hyaluronan and its derivatives attempt to increase the viscoelasticity of synovial fluid in osteoarthritic joints. These joints have lower concentrations of endogenous hyaluronic acid, resulting in loss of lubrication and less protection from mechanical stress.<100> Several double blind RCTs have demonstrated modest pain relief compared to placebo, in patients with mild to moderate OA of the knee after 3 to 5 weeks of weekly intra-articular hyaluronan injections.<101-106> Beneficial effects lasted up to 6 months in one of the studies.<105> One trial suggested benefit when hyaluronans are added to NSAID therapy.<106> However, two double blind RCTs found no benefit for intra-articular hyaluronan therapy over placebo <107,108>There have been no direct comparisons of the different hyaluronan derivatives. The least expensive hyaluronan is over $200 per course (3 injections).

Intra-articular hyaluronan may provide modest pain relief in mild to moderate OA of the knee. **This is a Grade B recommendation.**

The role of intra-articular hyaluronans in refractory osteoarthritis remains controversial.

Topical capsaicin may have modest benefit in a few patients but trials are few and not well done and many patients cannot tolerate the burning sensation produced by capsaicin. <109-111>

Surgical referral is based primarily on the patient's level of pain and degree of dysfunction while on optimal medical therapy.<112> Additional considerations include the age of the patient and the chance of prosthesis survival.<112> In most patients with OA of the knee or hip, total joint arthroplasty significantly improves functional status and health-related quality of life.<113,114>

Glucosamine sulfate is an alternative medicine proposed to stop the progression of cartilage breakdown in OA (i.e. chrondroprotection) and possibly reverse the process by stimulating production. However, there is no evidence at this time that glucosamine provides chondroprotection. Clinical studies to date, although suggesting some benefit for pain and mobility, are limited by poor design.<115-118> Furthermore, because alternative medicines are poorly regulated by Health Canada, there is no assurance that products sold as glucosamine actually contain any glucosamine. Therefore, the routine use of glucosamine sulfate cannot be recommended.

Table 3: Drug Therapy for Osteoarthritis

Agent	Evidence	Usual Dose	Cost/day	Comments
First-Line Therapy				
Acetaminophen	<28-30> <98>	325 mg qid prn - 1000 mg qid	$0.05-$0.12	***Effective analgesic in mild-moderate OA of the knee (not tested in OA of hip) and toxicity profile more favourable than NSAIDs.***
Second-Line Therapy				
NSAIDs	<29,30,98, 119-121>	See Table 4	See Table 4	***All NSAIDs have comparable efficacy in OA when equivalent doses are used. Dose requirements for OA are usually less than doses required to treat RA.***
OTHER THERAPIES				
Combination analgesics (e.g. acetaminophen with codeine)	<94,122, 123>	codeine dose: 60 mg bid – qid prn	$ 0.17 – $ 0.23	***Enhanced short-term analgesia when compared to acetaminophen alone but more adverse effects.***
Intra-articular corticosteroid injections (e.g. methylprednisolone, triamcinolone)	<96-99>	Methylprednisolone 4-80 mg q 4 months prn triamcinolone 5-40 mg q 4 months prn	$ 0.47 – $ 9.38 q dose (triamcin-olone not ODB)	***Short-term (4-6 week) decrease in pain and improvement in function in an inflamed knee.***
Intra-articular hyaluronans (e.g.,Suplasyn, Synvisc)	<101-105, 107, 124-125>	1 injection per week for 3-5 weeks	$240 - 385/ for 3 injections (not ODB)	***Modest decrease in pain for mild to moderate OA of the knee.***
Capsaicin cream (e.g., Zostrix)	<109-111>	Applied to affected area 3-4 times daily	$26 - $30 (not ODB)	***Modest decrease in pain.***

*Notes: See page 20

Intra-articular hyaluronan may provide modest pain relief in mild to moderate OA of the knee. **This is a Grade B recommendation.**

The role of intra-articular hyaluronans in refractory osteoarthritis remains controversial.

Topical capsaicin may have modest benefit in a few patients but trials are few and not well done and many patients cannot tolerate the burning sensation produced by capsaicin. <109-111>

Surgical referral is based primarily on the patient's level of pain and degree of dysfunction while on optimal medical therapy.<112> Additional considerations include the age of the patient and the chance of prosthesis survival.<112> In most patients with OA of the knee or hip, total joint arthroplasty significantly improves functional status and health-related quality of life.<113,114>

Glucosamine sulfate is an alternative medicine proposed to stop the progression of cartilage breakdown in OA (i.e. chrondroprotection) and possibly reverse the process by stimulating production. However, there is no evidence at this time that glucosamine provides chondroprotection. Clinical studies to date, although suggesting some benefit for pain and mobility, are limited by poor design.<115-118> Furthermore, because alternative medicines are poorly regulated by Health Canada, there is no assurance that products sold as glucosamine actually contain any glucosamine. Therefore, the routine use of glucosamine sulfate cannot be recommended.

Table 3: Drug Therapy for Osteoarthritis

Agent	Evidence	Usual Dose	Cost/day	Comments
First-Line Therapy				
Acetaminophen	<28-30> <98>	325 mg qid prn - 1000 mg qid	$0.05-$0.12	***Effective analgesic in mild-moderate OA of the knee (not tested in OA of hip) and toxicity profile more favourable than NSAIDs.***
Second-Line Therapy				
NSAIDs	<29,30,98, 119-121>	See Table 4	See Table 4	***All NSAIDs have comparable efficacy in OA when equivalent doses are used. Dose requirements for OA are usually less than doses required to treat RA.***
OTHER THERAPIES				
Combination analgesics (e.g. acetaminophen with codeine)	<94,122, 123>	codeine dose: 60 mg bid – qid prn	$ 0.17 – $ 0.23	***Enhanced short-term analgesia when compared to acetaminophen alone but more adverse effects.***
Intra-articular corticosteroid injections (e.g. methylprednisolone, triamcinolone)	<96-99>	Methylprednisolone 4-80 mg q 4 months prn triamcinolone 5-40 mg q 4 months prn	$ 0.47 – $ 9.38 q dose (triamcin-olone not ODB)	***Short-term (4-6 week) decrease in pain and improvement in function in an inflamed knee.***
Intra-articular hyaluronans (e.g.,Suplasyn, Synvisc)	<101-105, 107, 124-125>	1 injection per week for 3-5 weeks	$240 - 385/ for 3 injections (not ODB)	***Modest decrease in pain for mild to moderate OA of the knee.***
Capsaicin cream (e.g., Zostrix)	<109-111>	Applied to affected area 3-4 times daily	$26 - $30 (not ODB)	***Modest decrease in pain.***

*Notes: See page 20

Notes:

1. **Acetaminophen**
- Clinically significant drug interactions include: warfarin<126>, ethanol<32>, and perhaps phenytoin.<32> Maximum doses of acetaminophen may be lower in patients with serious liver or kidney disease.

2. **NSAIDs**
- Clinically significant drug interactions include: lithium, warfarin and methotrexate (rare).<32><127> NSAIDs are associated with a mild increase in supine blood pressure.<92>
- Patients at high-risk for GI bleeding should avoid NSAID use. High-risk is defined primarily by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAIDs cannot be avoided, high-risk patients should also receive misoprostol or a proton pump inhibitor <38><41-47,128> or a COX-2 NSAID considered. Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
- Informing patients of the risks has been associated with a lower incidence of acute GI bleeding.<129>
- Avoid in patients with history of ASA hypersensitivity.<93>

3. **Combination analgesics**
- May cause sedation and increase risk of falling and fracture in the elderly.<130>

4. **Intra-articular corticosteroid injections**
- Joint activity is usually minimized for 3 d following injection for theoretical reasons including: to enhance retention in the joint cavity and to prevent overuse of the affected joint. There is some evidence to suggest that this practice of joint rest is unnecessary.<131>
- Generally not administered more than 3-4 times/yr because of theoretical concern about progressive cartilage damage with repeated injection to weight-bearing joints.<6>

5. **Intra-articular hyaluronans**
- May cause transient pain and swelling on injection, usually lasting less than 4 days.
- Avoid in patients with chicken or egg allergy.

Table 4: Commonly Used NSAIDs

Drug	Brand Name	Milligrams per Day (frequency)†	Cost/day	ODB coverage
Low Cost per Dose Equivalent				
ASA (EC)	Aspirin Novasen Entrophen	2600 – 3900 (qid)	$ 0.10 - $ 0.18	Yes
Ibuprofen	Motrin Advil	1200-2400 (tid or qid)	$ 0.09 - $ 0.23	Yes
Indomethacin	Indocid	50 – 200 (bid or tid)	$ 0.17 - $ 0.60	Yes
Naproxen	Naprosyn	500 – 1000 (bid or tid)	$ 0.21 - $ 0.42	Yes
Medium Cost per Dose Equivalent				
Diclofenac	Voltaren	75-150 (bid or tid)	$ 0.59 - $ 1.18	Yes
Diflunisal	Dolobid	500 – 1000 (bid)	$ 0.85 - $ 1.04	Yes
Fenoprofen	Nalfon	600 – 2400 (tid or qid)	$ 0.57 - $ 2.07	Yes
Flurbiprofen	Ansaid Froben	150 – 200 (bid or tid)	$ 0.77 - $ 1.22	Yes
Ketoprofen	Orudis	150 – 200 (tid or qid)	$ 0.50 - $ 0.66	Yes
Piroxicam	Feldene	20 (daily)	$ 0.72	Yes
Sulindac	Clinoril	300 – 400 (bid)	$ 0.77 - $ 0.97	Yes
Tiaprofenic acid	Surgam	600 (bid or tid)	$ 0.82	Yes
High Cost per Dose Equivalent				
Diclofenac with misoprostol*	Arthrotec	100-150 of diclofenac (bid or tid)	$ 1.11 - $ 1.66	Yes
Etodolac	Ultradol	400 – 600 (daily or bid)	$ 1.60 - $ 2.40	No
Ketorolac	Toradol	20 – 40 (qid)	$ 1.29 - $ 2.59	No
Mefenamic acid	Ponstan	1000 (qid)	$ 1.32	Yes
Nabumetone	Relafen	1000 – 2000 (daily or bid)	$ 1.41 - $ 2.83	No
Oxaprozin	Daypro	600 – 1800 (daily or bid)	$ 0.69 - $ 2.06	No
Salsalate	Disalcid	1500 – 3000 (bid or tid)	$ 0.69 - $ 1.37	No
Tenoxicam	Mobiflex	20 (daily)	$ 1.28	No
Tolmetin	Tolectin	600 – 1800 (tid or qid)	$ 1.19 - $2.41	Yes
COX-2 Inhibiting NSAIDs				
Celecoxib	Celebrex	200-400 (daily or bid)	$1.25 - $2.50	Limited Use
Rofecoxib	Vioxx	12.5 – 50** (daily)	$1.25 - $2.50	Limited Use

ODB = Ontario Drug Benefit formulary

†daily = once daily; bid = twice daily; tid = three times daily; qid = four times daily

* Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>

** The higher dose of rofecoxib is reserved for acute pain indications.

Table 4: Commonly Used NSAIDs

Drug	Brand Name	Milligrams per Day (frequency)†	Cost/day	ODB coverage
Low Cost per Dose Equivalent				
ASA (EC)	Aspirin Novasen Entrophen	2600 – 3900 (qid)	$ 0.10 - $ 0.18	Yes
Ibuprofen	Motrin Advil	1200-2400 (tid or qid)	$ 0.09 - $ 0.23	Yes
Indomethacin	Indocid	50 – 200 (bid or tid)	$ 0.17 - $ 0.60	Yes
Naproxen	Naprosyn	500 – 1000 (bid or tid)	$ 0.21 - $ 0.42	Yes
Medium Cost per Dose Equivalent				
Diclofenac	Voltaren	75-150 (bid or tid)	$ 0.59 - $ 1.18	Yes
Diflunisal	Dolobid	500 – 1000 (bid)	$ 0.85 - $ 1.04	Yes
Fenoprofen	Nalfon	600 – 2400 (tid or qid)	$ 0.57 - $ 2.07	Yes
Flurbiprofen	Ansaid Froben	150 – 200 (bid or tid)	$ 0.77 - $ 1.22	Yes
Ketoprofen	Orudis	150 – 200 (tid or qid)	$ 0.50 - $ 0.66	Yes
Piroxicam	Feldene	20 (daily)	$ 0.72	Yes
Sulindac	Clinoril	300 – 400 (bid)	$ 0.77 - $ 0.97	Yes
Tiaprofenic acid	Surgam	600 (bid or tid)	$ 0.82	Yes
High Cost per Dose Equivalent				
Diclofenac with misoprostol*	Arthrotec	100-150 of diclofenac (bid or tid)	$ 1.11 - $ 1.66	Yes
Etodolac	Ultradol	400 – 600 (daily or bid)	$ 1.60 - $ 2.40	No
Ketorolac	Toradol	20 – 40 (qid)	$ 1.29 - $ 2.59	No
Mefenamic acid	Ponstan	1000 (qid)	$ 1.32	Yes
Nabumetone	Relafen	1000 – 2000 (daily or bid)	$ 1.41 - $ 2.83	No
Oxaprozin	Daypro	600 – 1800 (daily or bid)	$ 0.69 - $ 2.06	No
Salsalate	Disalcid	1500 – 3000 (bid or tid)	$ 0.69 - $ 1.37	No
Tenoxicam	Mobiflex	20 (daily)	$ 1.28	No
Tolmetin	Tolectin	600 – 1800 (tid or qid)	$ 1.19 - $2.41	Yes
COX-2 Inhibiting NSAIDs				
Celecoxib	Celebrex	200-400 (daily or bid)	$1.25 - $2.50	Limited Use
Rofecoxib	Vioxx	12.5 – 50** (daily)	$1.25 - $2.50	Limited Use

ODB = Ontario Drug Benefit formulary

†daily = once daily; bid = twice daily; tid = three times daily; qid = four times daily

* Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>

** The higher dose of rofecoxib is reserved for acute pain indications.

3.3 Osteoarthritis Bottom Lines

1. Nonpharmacologic interventions supported by evidence include: exercise<16-18>, exercise plus physiotherapy<19>, patient education for self-management<20,21> and social support<22-24>.
2. Patients may be referred or self-refer to The Arthritis Society to learn about additional resources. (see Appendix B)
3. Acetaminophen (maximum dose 1000 mg four times daily) is the agent of choice for analgesia in OA.<28-30>
4. Patients who are not adequately controlled with acetaminophen may progress to NSAIDs, advancing to higher doses as necessary.
5. Patients at high-risk for GI bleeding should avoid NSAID use including COX-2 NSAIDs. High-risk is defined primarily by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAID use cannot be avoided, patients should receive prophylaxis for GI bleeding with either misoprostol<38,41-43> or a proton pump inhibitor<43-47> or a switch to a COX-2 inhibiting NSAID considered. As prophylactic agents for serious GI events H_2 receptor antagonists are less effective then misoprostol or PPIs.<47,48,50> Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
6. The relative risk/benefit ratio for NSAIDs compared to acetaminophen plus codeine in OA is unclear.
7. Intra-articular corticosteroids effectively decrease pain and improve function in an inflamed painful knee.<96-99> These benefits last 4-6 weeks.
8. Intra-articular hyaluronans may produce moderate pain relief for mild to moderate OA of the knee.<101,104-106>
9. Surgical referral may be considered in patients who continue to experience significant pain and functional disability despite optimal medical therapy.<112>
10. Selective COX-2 inhibiting NSAIDs appear to have efficacy similar to other NSAIDs, with early evidence of a modest decrease in serious GI event rates. Risks for hypertension, renal and hepatic impairment are likely to be similar to older NSAIDs. Longterm safety of these drugs is unknown.

Section IV

Rheumatoid Arthritis

SECTION IV: RHEUMATOID ARTHRITIS

4.1 Overview

Rheumatoid arthritis is the most common systemic inflammatory disease, affecting approximately 0.5-2.5% of the adult population.<132,133> Long-term medical consequences of RA include radiographic disease progression, decline in functional status and premature mortality. Radiographic progression is observed in more than 50% of patients with RA within the first two years of disease onset. <132,134> Any drug that delays radiographic progression is regarded as altering the natural history of the disease. Functional status of a patient (i.e., ability to perform activities of daily living - ADLs) also declines more rapidly in the first several years of the disease.<132,135,136> RA has been associated with early mortality compared with age-matched controls who are free of the disease.<136-140> Poor clinical status has been identified as a predictor of early mortality.<140> Past estimates of the mortality and morbidity associated with RA may have been too low.<139> Long-term mortality rates in patients with severe RA approach those observed in patients with cardiovascular and neoplastic diseases.<141>

The goal of RA pharmacologic therapy is to delay progression of disease as assessed radiographically and to alleviate pain and suffering.

4.1.1 Epidemiology

Rheumatoid arthritis is estimated to have a prevalence between 0.5% and 2.5%.<132,133> The mean age of onset is 52 (± 15) years and females are affected more commonly than men at a ratio of 2-3:1.<3> Patients presenting with RA may have a wide spectrum of disease severity.<132> Some may present with a self-limiting polyarthritis that does not require long-term therapy, while others present with severe disease that progresses despite therapy; the majority of patients lie between these two ends of the spectrum.<132> Patients with severe disease often have positive rheumatoid factor, a high ESR or CRP, positive rheumatoid nodules and erosive changes on x-ray.<132,142,143>

4.1.2 Pathophysiology

The etiology of RA is unknown, but may involve a genetic predisposition and exposure to unknown environmental factors, such as infectious agents that can activate the body's immune system. Chronic inflammation of the synovial tissue lining the joint capsule is the underlying pathological process that creates the trademark painful joints in RA patients.

4.1.3 Clinical Presentation

The symptoms of RA normally develop insidiously over the course of several weeks to months. Table 5 highlights the diagnostic criteria for this condition.

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

micromedia
a division of IHS Canada

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

Table 5: 1987 Revised ARA Criteria for Diagnosis of RA <144>

Criteria	Definition
1. ***Morning stiffness***	Morning stiffness in and around the joints lasting ≥ 1 hour before maximal improvement
2. ***Arthritis of three or more joint areas***	At least three joint areas with soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joints areas are (right or left) PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. ***Arthritis of hand joints***	At least one joint area swollen in wrist, MCP, or PIP joint
4. ***Symmetric arthritis***	Bilateral involvement of PIP, MCP, or MTP joints
5. ***Rheumatoid nodules***	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
6. ***Serum rheumatoid factor***	Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive in less than 5% of normal control subjects
7. ***Radiographic changes***	Radiographic changes typical of RA on posteroanterior hand and wrist views, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (OA changes alone do not qualify)
* The diagnosis of RA is made when a patient has at least four of the above seven criteria. Criteria one through four must be present for at least six weeks.	

4.1.4 Assessment

Initial assessment: All patients in whom RA is strongly suspected should be considered for early DMARD therapy. Consistent use of DMARDs is associated with a better long-term disability index and early intervention with these agents is likely to have greatest impact on disease progression. <145-147>

Ongoing assessment: Periodic assessment of disease activity, drug toxicity and the effectiveness of therapy with revisions in the program as necessary, is essential.<7> Outcomes of interest for RA include: number of tender joints, number of swollen joints, pain, physician global assessment, patient global assessment, functional status, acute phase reactants and radiological damage.<148> It has been suggested that for an individual patient, an improvement of at least 17% is clinically important, depending on the outcome measure examined.<149>

Table 5: 1987 Revised ARA Criteria for Diagnosis of RA <144>

Criteria	*Definition*
1. ***Morning stiffness***	Morning stiffness in and around the joints lasting ≥ 1 hour before maximal improvement
2. ***Arthritis of three or more joint areas***	At least three joint areas with soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joints areas are (right or left) PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. ***Arthritis of hand joints***	At least one joint area swollen in wrist, MCP, or PIP joint
4. ***Symmetric arthritis***	Bilateral involvement of PIP, MCP, or MTP joints
5. ***Rheumatoid nodules***	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
6. ***Serum rheumatoid factor***	Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive in less than 5% of normal control subjects
7. ***Radiographic changes***	Radiographic changes typical of RA on posteroanterior hand and wrist views, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (OA changes alone do not qualify)
* The diagnosis of RA is made when a patient has at least four of the above seven criteria. Criteria one through four must be present for at least six weeks.	

4.1.4 Assessment

Initial assessment: All patients in whom RA is strongly suspected should be considered for early DMARD therapy. Consistent use of DMARDs is associated with a better long-term disability index and early intervention with these agents is likely to have greatest impact on disease progression. <145-147>

Ongoing assessment: Periodic assessment of disease activity, drug toxicity and the effectiveness of therapy with revisions in the program as necessary, is essential.<7> Outcomes of interest for RA include: number of tender joints, number of swollen joints, pain, physician global assessment, patient global assessment, functional status, acute phase reactants and radiological damage.<148> It has been suggested that for an individual patient, an improvement of at least 17% is clinically important, depending on the outcome measure examined.<149>

48 45

4.2 Treatment of Rheumatoid Arthritis

4.2.1 Nonpharmacologic Therapy

Nonpharmacologic therapy is important in the management of patients with RA. Those supported by good quality evidence include: exercise<150,151> and patient education for self-management<20,21,152>. Assessment regarding optimal rehabilitation is also important.

Dynamic exercise (e.g. aerobic pool and walking exercises, bicycle training) improves aerobic capacity, muscle strength and joint mobility without adversely affecting pain.<150,151> The physician, physiotherapist and/or occupational therapist, and the patient must be aware that the physical component of therapy demands re-evaluation as the disease evolves and flares up.<7> Attendance in programs such as an arthritis self-management program can decrease pain, decrease frequency of physician visits, and provide an overall improvement in quality of life.<20,21,152> More information about these programs can be obtained by contacting The Arthritis Society (see Appendix B). A community-based physical therapy program for RA that combines education and exercise has been shown to improve patient self-efficacy, disease management knowledge and morning stiffness.<153>

4.2.2 Pharmacologic Therapy

As no cure is known for RA, the goals of therapy are to control symptoms (e.g., stiffness and pain) and delay disease progression to irreversible joint damage.<7>

Meta-analyses of RCTs show that **DMARDs** reduce symptoms of inflammatory synovitis such as numbers of swollen and tender joints.<154-157> There is also reasonable evidence that DMARDs reduce the long-term disability associated with RA. One study assessed almost 3000 patients with RA followed for an average of nine years. Consistent use of DMARDs (various used) was associated with a better long-term disability index (determined by the Health Assessment Questionnaire), and this effect occurred over all periods of disease duration.<145> In this trial, NSAIDs and prednisone failed to show this disability benefit.<145> The results of this study suggest that DMARDs may reduce long-term disability by up to 30%. Another recent trial evaluated the impact of withdrawing DMARD therapy in patients who were well controlled. <158> When patients were given placebo instead of their DMARD, flare up of the disease occurred in a substantial number. This finding illustrates that RA remains chronic despite suppression with DMARDs and that long-term DMARD therapy is necessary.<158> Because of potential toxicity, regular surveillance of patients on DMARDs therapy is recommended. (Table 8)

Combination DMARD therapy is now well supported by RCT evidence for RA particularly early RA and may be cost-effective compared to single DMARD therapy. <159-164> Rates of remission and delays in radiologic progression are superior without significant increases in toxicity.<164>

Consistent use of DMARDs is associated with a better long-term disability index and early intervention with these agents is likely to have greatest impact on disease progression. <145-147> Combination DMARD therapy can be recommended particularly for early RA based on improved remission rates.

This is a Grade A recommendation.

While patients with mild disease may have symptoms controlled with NSAIDs<132>, it is essential that all patients be evaluated for early DMARD therapy to delay irreversible joint damage.<146,147> The risks and benefits related to NSAIDs including COX-2 inhibiting NSAIDs as previously outlined, apply to RA patients.

NSAIDs provide symptom control such as reducing joint pain, joint tenderness and morning stiffness but they do not alter the course of the RA. They are only recommended as symptom relief once DMARD therapy has been organized.

This is a Grade B recommendation.

The role of **corticosteroids (oral and intra-articular)** remains controversial.<7> Despite their wide-spread use, there are sparse data on their effectiveness in RA.<165,166> Short-term, low-dose (≤ 15 mg/day) oral prednisone may be useful as "bridge therapy", to reduce symptoms before DMARD therapy has taken effect or as adjunct therapy in patients not adequately controlled despite DMARD and NSAID use.<165> The adverse effects of corticosteroids limit their use, especially if given at higher doses or for extended periods of time. Limited evidence and extensive clinical experience suggest intra-articular steroids are useful to treat disease flares.<167,168>

Corticosteroids, given orally or intra-articularly, are useful short-term adjunctive agents for patients who are not adequately controlled with NSAIDs and DMARDs.

This is a Grade B recommendation.

Although the available data regarding administration of opioid therapy in patients with rheumatoid arthritis suggest that it may be beneficial in some cases, they are not recommended to be administered on chronic basis until other analgesic therapies have failed. <169>

4.2 Treatment of Rheumatoid Arthritis

4.2.1 Nonpharmacologic Therapy

Nonpharmacologic therapy is important in the management of patients with RA. Those supported by good quality evidence include: exercise<150,151> and patient education for self-management<20,21,152>. Assessment regarding optimal rehabilitation is also important.

Dynamic exercise (e.g. aerobic pool and walking exercises, bicycle training) improves aerobic capacity, muscle strength and joint mobility without adversely affecting pain.<150,151> The physician, physiotherapist and/or occupational therapist, and the patient must be aware that the physical component of therapy demands re-evaluation as the disease evolves and flares up.<7> Attendance in programs such as an arthritis self-management program can decrease pain, decrease frequency of physician visits, and provide an overall improvement in quality of life.<20,21,152> More information about these programs can be obtained by contacting The Arthritis Society (see Appendix B). A community-based physical therapy program for RA that combines education and exercise has been shown to improve patient self-efficacy, disease management knowledge and morning stiffness.<153>

4.2.2 Pharmacologic Therapy

As no cure is known for RA, the goals of therapy are to control symptoms (e.g., stiffness and pain) and delay disease progression to irreversible joint damage.<7>

Meta-analyses of RCTs show that **DMARDs** reduce symptoms of inflammatory synovitis such as numbers of swollen and tender joints.<154-157> There is also reasonable evidence that DMARDs reduce the long-term disability associated with RA. One study assessed almost 3000 patients with RA followed for an average of nine years. Consistent use of DMARDs (various used) was associated with a better long-term disability index (determined by the Health Assessment Questionnaire), and this effect occurred over all periods of disease duration.<145> In this trial, NSAIDs and prednisone failed to show this disability benefit.<145> The results of this study suggest that DMARDs may reduce long-term disability by up to 30%. Another recent trial evaluated the impact of withdrawing DMARD therapy in patients who were well controlled. <158> When patients were given placebo instead of their DMARD, flare up of the disease occurred in a substantial number. This finding illustrates that RA remains chronic despite suppression with DMARDs and that long-term DMARD therapy is necessary.<158> Because of potential toxicity, regular surveillance of patients on DMARDs therapy is recommended. (Table 8)

Combination DMARD therapy is now well supported by RCT evidence for RA particularly early RA and may be cost-effective compared to single DMARD therapy. <159-164> Rates of remission and delays in radiologic progression are superior without significant increases in toxicity.<164>

Consistent use of DMARDs is associated with a better long-term disability index and early intervention with these agents is likely to have greatest impact on disease progression. <145-147> Combination DMARD therapy can be recommended particularly for early RA based on improved remission rates.

This is a Grade A recommendation.

While patients with mild disease may have symptoms controlled with NSAIDs<132>, it is essential that all patients be evaluated for early DMARD therapy to delay irreversible joint damage.<146,147> The risks and benefits related to NSAIDs including COX-2 inhibiting NSAIDs as previously outlined, apply to RA patients.

NSAIDs provide symptom control such as reducing joint pain, joint tenderness and morning stiffness but they do not alter the course of the RA. They are only recommended as symptom relief once DMARD therapy has been organized.

This is a Grade B recommendation.

The role of **corticosteroids (oral and intra-articular)** remains controversial.<7> Despite their wide-spread use, there are sparse data on their effectiveness in RA.<165,166> Short-term, low-dose (≤ 15 mg/day) oral prednisone may be useful as "bridge therapy", to reduce symptoms before DMARD therapy has taken effect or as adjunct therapy in patients not adequately controlled despite DMARD and NSAID use.<165> The adverse effects of corticosteroids limit their use, especially if given at higher doses or for extended periods of time. Limited evidence and extensive clinical experience suggest intra-articular steroids are useful to treat disease flares.<167,168>

Corticosteroids, given orally or intra-articularly, are useful short-term adjunctive agents for patients who are not adequately controlled with NSAIDs and DMARDs.

This is a Grade B recommendation.

Although the available data regarding administration of opioid therapy in patients with rheumatoid arthritis suggest that it may be beneficial in some cases, they are not recommended to be administered on chronic basis until other analgesic therapies have failed. <169>

Table 6: Drug Therapy for Rheumatoid Arthritis

Agent	Evidence	Usual Dose	Cost	Comments
First-Line Therapy				
DMARDs	<143,145, 170>	See Table 7	See Table 7	***Most effective agents for patients with active disease as they have been shown to reduce long-term disability.***
Second-Line Therapy				
NSAIDs	<171>	See Table 4	See Table 4	***All NSAIDs have comparable efficacy in RA.***
Prednisone	<172>	5 - 20 mg	$ 0.01 - $ 0.04	
Other Therapies				
Intra-articular corticosteroid injections (e.g. methylprednisolone, triamcinolone)	<167,168>	Methylprednisolone 4-80 mg q 4 months prn Triamcinolone 5-40 mg q 4 months prn	$ 0.47 – $ 9.38 per dose (triamcinolone not ODB)	***Limited data and extensive clinical experience suggest that these agents are useful as an adjunct to usual therapy.***

NOTES:

1. **DMARDs**
- Important to start therapy early in disease process.<146,147>
- No DMARD proven as most effective. The decision about which DMARD(s) to use is influenced by the patient's clinical disease activity, functional status, age, underlying medical status and lifestyle (including plans for conception and alcohol use). Combination DMARDs should be considered.
- Recent data suggest combination DMARD therapy may be more efficacious than monotherapy.<159,161,162> Combinations including methotrexate and sulfasalazine are the best studied.<159,161,163>
- Relative teratogenecity of DMARDs should be considered by women of child-bearing potential.

2. **NSAIDs**
- Clinically significant drug interactions include: lithium, warfarin and methotrexate (rare).<32><127> NSAIDs are associated with a mild increase in supine blood pressure.<92>
- Patients at high-risk for GI bleeding should avoid NSAID use. High-risk is defined primarily by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAIDs can not be avoided, high-risk patients should also receive misoprostol or a proton pump inhibitor<38><41>.<42-47,128> or a COX-2 NSAID considered. Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
- Informing patients of the risks has been associated with a lower incidence of acute GI bleeding.<129>
- Avoid in patients with history of ASA hypersensitivity.<93>

3. **Prednisone**
- The prevention and treatment of osteoporosis due to prolonged corticosteroid use requires additional medical management.<173>
- RCTs have failed to find a significant increase in serious GI events when corticosteroids are taken with NSAIDs.<38>

4. **Intra-articular corticosteroid injections**
- Joint activity is usually minimized for 3 d following injection for several theoretical reasons: to enhance retention in the joint cavity and to prevent overuse of the affected joint. There is some evidence to suggest that this practice of joint rest is unnecessary.<131>
- Generally not administered more than 3-4 times/yr because of theoretical concern about progressive cartilage damage with repeated injection to weight-bearing joints.<6>

Table 7: Commonly Used DMARDs

Drug	Usual Dose†	Cost/day ‡	Comments
Azathioprine (e.g. Imuran)	50-100mg PO daily; max of 2.5mg/kg daily	$ 0.60 - $ 1.20	• Long-term risk of malignancy not proven<174>
Cyclosporine (e.g., Neoral)	2.5-5.0mg/kg PO daily	$ 9.95 - $ 19.90 (Limited Use Status)	• Studied in patients with very severe, refractory active RA
Gold injectable: aurothiomalate, aurothioglucose (e.g., Myochrysine Solganal)	Test dose: 10mg IM, then 25mg IM one week later Maintenance dose: 50mg IM/week	Aurothiomalate $ 2.43* aurothioglucose $ 1.53	• Dosing interval can be increased to every 3-4 weeks if there is a positive response
Gold oral: auranofin (e.g., Ridaura)	3-6 mg PO daily	$1.26 - $ 2.52	• Onset slower (4-6 months) than other DMARDs <7>
Hydroxychloroquine (e.g. Plaquenil)	200-400mg PO daily; max of 5-6mg/kg daily	$ 0.52 - $ 1.05	• Risk factors for retinal toxicity appear to be a combination of cumulative dose (> 800 gm) and age >70 years <93>
Methotrexate (e.g., Rheumatrex)	7.5-25 mg PO/ IM/SC weekly	$ 0.43 - $ 1.14	• Onset faster (6-8 weeks) than other DMARDs <7> • Low dose folate supplementation (1-5 mg/day) reduces GI and mucocutaneous toxicities by 80% without increasing disease activity<175> • avoid use of trimethoprim because of increased risk for toxicity • Alcohol intake should be restricted (<2 drinks/week) to minimize hepatic injury <93>
D-Penicillamine (e.g., Cuprimine)	125-250mg PO daily, then ↑ doses to max of 750-1000mg daily	$ 0.49 - $ 3.92	• Slow increase in dosage may reduces incidence of thrombocytopenia<93>
Sulfasalazine (e.g. Salazopyrin)	500mg PO daily, then ↑ doses to a max of 3000mg daily	$ 0.11 - $ 2.58	• Slow increase in dosage may reduce GI toxicity • Avoid in patients with hypersensitivity reactions to sulfa drugs <93>

† PO - oral; IM - intramuscular; SC – subcutaneous.

‡ All agents are covered by Ontario Drug Benefit Formulary (ODB) but cyclosporine is restricted to limited use. Costs of monitoring drug therapy may be taken into account when selecting a drug.

* Based on weekly injections.

Table 6: Drug Therapy for Rheumatoid Arthritis

Agent	Evidence	Usual Dose	Cost	Comments
First-Line Therapy				
DMARDs	<143,145, 170>	See Table 7	See Table 7	***Most effective agents for patients with active disease as they have been shown to reduce long-term disability.***
Second-Line Therapy				
NSAIDs	<171>	See Table 4	See Table 4	***All NSAIDs have comparable efficacy in RA.***
Prednisone	<172>	5 - 20 mg	$ 0.01 - $ 0.04	
Other Therapies				
Intra-articular corticosteroid injections (e.g. methylprednisolone, triamcinolone)	<167,168>	Methylprednisolone 4-80 mg q 4 months prn Triamcinolone 5-40 mg q 4 months prn	$ 0.47 – $ 9 38 per dose (triamcinolone not ODB)	***Limited data and extensive clinical experience suggest that these agents are useful as an adjunct to usual therapy.***

NOTES:

1. **DMARDs**
- Important to start therapy early in disease process.<146,147>
- No DMARD proven as most effective. The decision about which DMARD(s) to use is influenced by the patient's clinical disease activity, functional status, age, underlying medical status and lifestyle (including plans for conception and alcohol use). Combination DMARDs should be considered.
- Recent data suggest combination DMARD therapy may be more efficacious than monotherapy.<159,161,162> Combinations including methotrexate and sulfasalazine are the best studied.<159,161,163>
- Relative teratogenecity of DMARDs should be considered by women of child-bearing potential.

2. **NSAIDs**
- Clinically significant drug interactions include: lithium, warfarin and methotrexate (rare).<32><127> NSAIDs are associated with a mild increase in supine blood pressure.<92>
- Patients at high-risk for GI bleeding should avoid NSAID use. High-risk is defined primarily by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAIDs can not be avoided, high-risk patients should also receive misoprostol or a proton pump inhibitor<38><41>,<42-47,128> or a COX-2 NSAID considered. Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
- Informing patients of the risks has been associated with a lower incidence of acute GI bleeding.<129>
- Avoid in patients with history of ASA hypersensitivity.<93>

3. **Prednisone**
- The prevention and treatment of osteoporosis due to prolonged corticosteroid use requires additional medical management.<173>
- RCTs have failed to find a significant increase in serious GI events when corticosteroids are taken with NSAIDs.<38>

4. **Intra-articular corticosteroid injections**
- Joint activity is usually minimized for 3 d following injection for several theoretical reasons: to enhance retention in the joint cavity and to prevent overuse of the affected joint. There is some evidence to suggest that this practice of joint rest is unnecessary.<131>
- Generally not administered more than 3-4 times/yr because of theoretical concern about progressive cartilage damage with repeated injection to weight-bearing joints.<6>

Table 7: Commonly Used DMARDs

Drug	Usual Dose†	Cost/day ‡	Comments
Azathioprine (e.g. Imuran)	50-100mg PO daily; max of 2.5mg/kg daily	$ 0.60 - $ 1.20	• Long-term risk of malignancy not proven<174>
Cyclosporine (e.g., Neoral)	2.5-5.0mg/kg PO daily	$ 9.95 - $ 19.90 (Limited Use Status)	• Studied in patients with very severe, refractory active RA
Gold injectable: aurothiomalate, aurothioglucose (e.g., Myochrysine Solganal)	Test dose: 10mg IM, then 25mg IM one week later Maintenance dose: 50mg IM/week	Aurothiomalate $ 2.43* aurothioglucose $ 1.53	• Dosing interval can be increased to every 3-4 weeks if there is a positive response
Gold oral: auranofin (e.g., Ridaura)	3-6 mg PO daily	$1.26 - $ 2.52	• Onset slower (4-6 months) than other DMARDs <7>
Hydroxychloroquine (e.g. Plaquenil)	200-400mg PO daily; max of 5-6mg/kg daily	$ 0.52 - $ 1.05	• Risk factors for retinal toxicity appear to be a combination of cumulative dose (> 800 gm) and age >70 years <93>
Methotrexate (e.g., Rheumatrex)	7.5-25 mg PO/ IM/SC weekly	$ 0.43 - $ 1.14	• Onset faster (6-8 weeks) than other DMARDs <7> • Low dose folate supplementation (1-5 mg/day) reduces GI and mucocutaneous toxicities by 80% without increasing disease activity<175> • avoid use of trimethoprim because of increased risk for toxicity • Alcohol intake should be restricted (<2 drinks/week) to minimize hepatic injury <93>
D-Penicillamine (e.g., Cuprimine)	125-250mg PO daily, then ↑ doses to max of 750-1000mg daily	$ 0.49 - $ 3.92	• Slow increase in dosage may reduces incidence of thrombocytopenia<93>
Sulfasalazine (e.g. Salazopyrin)	500mg PO daily, then ↑ doses to a max of 3000mg daily	$ 0.11 - $ 2.58	• Slow increase in dosage may reduce GI toxicity • Avoid in patients with hypersensitivity reactions to sulfa drugs <93>

† PO - oral; IM - intramuscular; SC – subcutaneous.

‡ All agents are covered by Ontario Drug Benefit Formulary (ODB) but cyclosporine is restricted to limited use. Costs of monitoring drug therapy may be taken into account when selecting a drug.

* Based on weekly injections.

Table 8: Adverse Effects and Suggested Monitoring of DMARDs (Adapted from <176>)

Drug	Common Adverse Effects*	Uncommon Adverse Effects*	Rare Adverse Effects*	Monitoring (suggested initial frequency)
Azathioprine	• GI	• rash	• cytopenias • pancreatitis • ↑ LFTs	CBC (2-4 w) Platelets (2-4 w) LFTs (2-4 w)
Cyclosporine	• gingival hyperplasia • hypertension • hirsutism	• nephro-toxicity	• cytopenias	Creatinine (2-4 w) CBC Platelets BP
Gold, injectable	• rash • stomatitis • proteinuria	• thrombocyt-openia	• aplastic anemia • nephrotic syndrome	CBC (1-4 w) Urinalysis (1-4 w)
Gold, oral	• diarrhea • rash • stomatitis		• cytopenias (less than IM gold) • proteinuria • nephrotic syndrome(less than IM gold)	CBC (4-12 w) Urinalysis (4-12 w)
Hydroxychloroquine			• retinal damage • GI	Fundoscopy and visual fields (6 m)
Methotrexate	• GI • mucositis • ↑ LFTs	• pneumonitis • cytopenias	• hepatic cirrhosis • hepatic fibrosis	CBC (4-8 w) Platelets (4-8 w) LFTs (4-8 w) Creatinine (4-8 w) Shortness of breath
D-Penicillamine	• rash • stomatitis • dysgeusia		• cytopenias • proteinuria • nephrotic syndrome • autoimmune syndromes	CBC (4-8 w) Platelets (4-8 w) Urinalysis (4-8 w)
Sulfasalazine	• GI • mucositis • CNS	• leukopenia • rash	• ↑ LFTs • cytopenias	LFTs (4-8 w) CBC (4-8 w) Platelets (4-8 w)

*Common = frequency of adverse effect > 10%; Uncommon = frequency of adverse effects 1- 10 %;
Rare = frequency of adverse effect <1%.
GI = gastrointestinal including nausea, vomiting, anorexia, diarrhea; LFTs = liver function tests; CNS = central nervous system including headache, irritability, dizziness.

Table 8: Adverse Effects and Suggested Monitoring of DMARDs (Adapted from <176>)

Drug	Common Adverse Effects*	Uncommon Adverse Effects*	Rare Adverse Effects*	Monitoring (suggested initial frequency)
Azathioprine	• GI	• rash	• cytopenias • pancreatitis • ↑ LFTs	CBC (2-4 w) Platelets (2-4 w) LFTs (2-4 w)
Cyclosporine	• gingival hyperplasia • hypertension • hirsutism	• nephro-toxicity	• cytopenias	Creatinine (2-4 w) CBC Platelets BP
Gold, injectable	• rash • stomatitis • proteinuria	• thrombocyt-openia	• aplastic anemia • nephrotic syndrome	CBC (1-4 w) Urinalysis (1-4 w)
Gold, oral	• diarrhea • rash • stomatitis		• cytopenias (less than IM gold) • proteinuria • nephrotic syndrome(less than IM gold)	CBC (4-12 w) Urinalysis (4-12 w)
Hydroxychloroquine			• retinal damage • GI	Fundoscopy and visual fields (6 m)
Methotrexate	• GI • mucositis • ↑ LFTs	• pneumonitis • cytopenias	• hepatic cirrhosis • hepatic fibrosis	CBC (4-8 w) Platelets (4-8 w) LFTs (4-8 w) Creatinine (4-8 w) Shortness of breath
D-Penicillamine	• rash • stomatitis • dysgeusia		• cytopenias • proteinuria • nephrotic syndrome • autoimmune syndromes	CBC (4-8 w) Platelets (4-8 w) Urinalysis (4-8 w)
Sulfasalazine	• GI • mucositis • CNS	• leukopenia • rash	• ↑ LFTs • cytopenias	LFTs (4-8 w) CBC (4-8 w) Platelets (4-8 w)

*Common = frequency of adverse effect > 10%; Uncommon = frequency of adverse effects 1- 10 %;
Rare = frequency of adverse effect <1%.
GI = gastrointestinal including nausea, vomiting, anorexia, diarrhea; LFTs = liver function tests; CNS = central nervous system including headache, irritability, dizziness.

4.3 Rheumatoid Arthritis Bottom Lines

1. Non-pharmacologic therapies supported by evidence include exercise<150,151> and patient education.<20,21,152>
2. Early consultation with an arthritis specialist is recommended to confirm diagnosis and treatment.
3. All patients in whom RA is strongly suspected should be considered for early DMARD therapy, including combination DMARD therapy.<146,147>
4. DMARDs have toxicities that require monitoring. The frequency of monitoring varies depending on the drugs used. Good communication between family physician and specialist is essential during this therapy.
5. All NSAIDs have comparable effect on symptoms in RA but do not alter disease progression. Patients at high-risk for GI bleeding should avoid NSAID use including COX-2 NSAIDs. High-risk is defined by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAID use can not be avoided, patients should receive prophylaxis for GI bleeding with either misoprostol <38,41-43> or a proton pump inhibitor <43-47> or a switch to a COX-2 inhibiting NSAID considered. The H_2 receptor antagonists are inferior to misoprostol and PPI as prophylactic agents.<47,48,50> Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
6. Corticosteroids, given orally or intra-articularly, are useful adjunctive agents for patients who are not adequately controlled with NSAIDs and DMARDs.<172>
7. Referral of patients to The Arthritis Society may allow them to learn about additional resources. (See Appendix B)

Section V

Acute Soft-Tissue Disorders

SECTION V: ACUTE SOFT TISSUE DISORDERS

5.1 Overview

Most soft tissue injuries are caused by one of two mechanisms: single-impact macrotrauma (acute injury) or repetitive microtrauma (overuse, or chronic injury).<177> This section focuses on acute musculoskeletal injuries, which are often sudden and traumatic, resulting from a single twist or blow. These injuries can range from catastrophic injuries (involving major structural damage to bone or cartilage) to relatively minor soft tissue injuries. This section will further focus on relatively minor injuries such as strains and sprains.

Ligaments are fibrous connective tissue joining bones or cartilage, providing strength and support to joints. Sprains are injuries that involve rupturing or tearing of ligament fibers. On the other hand, strains result from over-stretching or overexertion of parts of the musculature or a muscle-tendon unit.<178>

5.2 Treatment of Acute Soft Tissue Disorders

Although an extremely common diagnosis, there is a surprising lack of high quality evidence regarding the management of acute soft-tissue disorders. This may be mainly due to the generally good prognosis with simple supportive therapies.<179>

5.2.1 Nonpharmacologic Therapy

The care of acute soft tissue injuries involves rapid immobilization and assessment of the possibility of major structural damage, such as fracture. Identifiable predisposing or causative factors should be modified in order to decrease future risks.<180> Since acute soft-tissue injuries often bleed and cause swelling, initial treatment is designed to limit these complications. The simplest regimen includes rest, ice, compression, and elevation (RICE).<179> For most common injuries, this program is continued for 24-72 hours and is followed by a guided program of mobilization and rehabilitation until the individual is ready to resume his or her usual activities. Use of passive modalities, such as ultrasound, TENS and diathermy in acute MSK injury is not supported by evidence.<25,181>

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

micromedia
a division of IHS Canada

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

5.2.2 Pharmacologic Therapy

The goal of pharmacological therapy is to reduce acute symptoms, specifically pain. Therefore, treatment periods should be of short duration.

Acetaminophen (maximum dose 4g/day) is the analgesic of choice, based on its favourable benefit: risk profile. Efficacy data on acetaminophen has been extrapolated from postoperative pain models.<182>

For pain relief in acute soft tissue disorders, acetaminophen is recommended as the analgesic of choice.

This is a Grade D recommendation.

Numerous small RCTs have demonstrated that **NSAIDs** provide superior short-term pain relief for acute soft tissue disorders, when compared to placebo.<181,183-192> NSAID therapy may also allow patients to return to full activities faster than no drug therapy, however this is most likely due to their analgesic effects. Long-term outcomes, such as joint stability, are not altered by NSAID therapy. There is no information on the efficacy of COX-2 inhibiting NSAIDs in acute musculoskeletal injury to make any firm recommendation. Short term use of NSAIDs for acute MSK injury is thought to confer less risk of GI toxicity than chronic use. Therefore the COX-2 inhibiting NSAIDs are likely to be less cost-effective overall in acute compared to chronic MSK conditions.

NSAIDs provide adequate analgesia for acute soft tissue disorders. Serious GI toxicity is the major concern.

This is a Grade B recommendation.

No studies comparing **combination analgesics** (e.g. acetaminophen with codeine) to placebo in acute soft tissue disorders were identified. Three small RCTs suggest that combination analgesics are comparable to NSAIDs for relieving pain in patients with acute MSK injury. <193-195>

Combination analgesics provide short-term analgesia in acute soft tissue disorders. Compared to acetaminophen alone, they have more adverse effects.

This is a Grade B recommendation.

Skeletal muscle relaxants are not recommended for routine use in acute MSK injury due to their marginal efficacy in providing pain relief and significant side effect profile. These agents have sedative properties that can impair psychomotor function and driving skills, especially in the elderly.<196>

Skeletal muscle relaxants are not recommended because of limited evidence of efficacy and concern regarding psychomotor impairment.

This is a Grade D recommendation.

5.2.2 Pharmacologic Therapy

The goal of pharmacological therapy is to reduce acute symptoms, specifically pain. Therefore, treatment periods should be of short duration.

Acetaminophen (maximum dose 4g/day) is the analgesic of choice, based on its favourable benefit: risk profile. Efficacy data on acetaminophen has been extrapolated from postoperative pain models.<182>

For pain relief in acute soft tissue disorders, acetaminophen is recommended as the analgesic of choice.

This is a Grade D recommendation.

Numerous small RCTs have demonstrated that **NSAIDs** provide superior short-term pain relief for acute soft tissue disorders, when compared to placebo.<181,183-192> NSAID therapy may also allow patients to return to full activities faster than no drug therapy, however this is most likely due to their analgesic effects. Long-term outcomes, such as joint stability, are not altered by NSAID therapy. There is no information on the efficacy of COX-2 inhibiting NSAIDs in acute musculoskeletal injury to make any firm recommendation. Short term use of NSAIDs for acute MSK injury is thought to confer less risk of GI toxicity than chronic use. Therefore the COX-2 inhibiting NSAIDs are likely to be less cost-effective overall in acute compared to chronic MSK conditions.

NSAIDs provide adequate analgesia for acute soft tissue disorders. Serious GI toxicity is the major concern.

This is a Grade B recommendation.

No studies comparing **combination analgesics** (e.g. acetaminophen with codeine) to placebo in acute soft tissue disorders were identified. Three small RCTs suggest that combination analgesics are comparable to NSAIDs for relieving pain in patients with acute MSK injury. <193-195>

Combination analgesics provide short-term analgesia in acute soft tissue disorders. Compared to acetaminophen alone, they have more adverse effects.

This is a Grade B recommendation.

Skeletal muscle relaxants are not recommended for routine use in acute MSK injury due to their marginal efficacy in providing pain relief and significant side effect profile. These agents have sedative properties that can impair psychomotor function and driving skills, especially in the elderly.<196>

Skeletal muscle relaxants are not recommended because of limited evidence of efficacy and concern regarding psychomotor impairment.

This is a Grade D recommendation.

Table 9: Drug Therapy for Acute Soft Tissue Disorders

Agent	Evidence	Usual Dose*	Cost/day	Comments
First-Line Therapy				
Acetaminophen	<182>	325 mg qid prn - 1000 mg qid	$ 0.05 - $ 0.12	***Effective analgesia demonstrated in postoperative pain models. Toxicity profile more favourable than NSAIDs.***
Second-Line Therapy				
NSAIDs	<181,183-192><197><198>	See Table 4	See Table 4	***Superior to placebo for short term pain relief in acute MSK injuries. May allow faster return to full activity than no drug therapy, but this is most likely due to the analgesic effect.***
Combination analgesics (e.g. acetaminophen with codeine)	<193-195>	codeine dose: 60 mg bid – qid prn	$ 0.17 – $ 0.23	***No placebo controlled trials in acute MSK injury. Comparable efficacy to NSAID for pain relief in acute injuries.***

Notes:

1. **Acetaminophen**
- Clinically significant drug interactions include: warfarin<126>, ethanol<32> and perhaps phenytoin.<32> Maximum doses of acetaminophen may be lower in patients with serious liver or kidney disease.

2. **NSAIDs**
- Clinically significant drug interactions include: lithium, warfarin and methotrexate (rare).<32><127> NSAIDs are associated with a mild increase in supine blood pressure. <92>
- Patients at high-risk for GI bleeding should avoid NSAID use. High-risk is defined primarily by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAIDs can not be avoided, high-risk patients should also receive misoprostol or a proton pump inhibitor <38> <41-47,128> or a COX-2 NSAID considered. Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
- Informing patients of the risks has been associated with a lower incidence of acute GI bleeding.<129>
- Avoid in patients with history of ASA hypersensitivity.<93>

3. **Combination analgesics**
- May cause sedation and increase risk of falling and fracture in the elderly.<130>
- Acetaminophen with codeine causes significantly more dizziness, nausea, vomiting and constipation than acetaminophen alone.<122>

Table 9: Drug Therapy for Acute Soft Tissue Disorders

Agent	Evidence	Usual Dose*	Cost/day	Comments
First-Line Therapy				
Acetaminophen	<182>	325 mg qid prn - 1000 mg qid	$ 0.05 - $ 0.12	***Effective analgesia demonstrated in postoperative pain models. Toxicity profile more favourable than NSAIDs.***
Second-Line Therapy				
NSAIDs	<181,183-192><197> <198>	See Table 4	See Table 4	***Superior to placebo for short term pain relief in acute MSK injuries. May allow faster return to full activity than no drug therapy, but this is most likely due to the analgesic effect.***
Combination analgesics (e.g. acetaminophen with codeine)	<193-195>	codeine dose: 60 mg bid – qid prn	$ 0.17 – $ 0.23	***No placebo controlled trials in acute MSK injury. Comparable efficacy to NSAID for pain relief in acute injuries.***

Notes:

1. **Acetaminophen**
- Clinically significant drug interactions include: warfarin<126>, ethanol<32> and perhaps phenytoin.<32> Maximum doses of acetaminophen may be lower in patients with serious liver or kidney disease.

2. **NSAIDs**
- Clinically significant drug interactions include: lithium, warfarin and methotrexate (rare).<32><127> NSAIDs are associated with a mild increase in supine blood pressure. <92>
- Patients at high-risk for GI bleeding should avoid NSAID use. High-risk is defined primarily by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAIDs can not be avoided, high-risk patients should also receive misoprostol or a proton pump inhibitor <38> <41-47,128> or a COX-2 NSAID considered. Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
- Informing patients of the risks has been associated with a lower incidence of acute GI bleeding.<129>
- Avoid in patients with history of ASA hypersensitivity.<93>

3. **Combination analgesics**
- May cause sedation and increase risk of falling and fracture in the elderly.<130>
- Acetaminophen with codeine causes significantly more dizziness, nausea, vomiting and constipation than acetaminophen alone.<122>

5.3 Acute Soft Tissue Disorders Bottom Lines

1. In the initial 24-72 hours after injury, an analgesic may be combined with rest, ice, compression, and elevation to provide pain relief, reduce swelling, and combat hemorrhage. Acetaminophen (max. dose 4g/d) is the analgesic of choice to relieve pain.
2. Nonsteroidal anti-inflammatory drugs (NSAIDs) provide short-term pain relief in acute MSK injury. <181,183-192,197,198> Return to full activities may also be faster with NSAID use as compared to placebo, although this is most likely due to their analgesic effect. <181,187,190> Early NSAID use does not alter long term outcomes, such as joint stability.<181>
3. There are no trials that compare combination analgesics (e.g. acetaminophen with codeine) to placebo<195>. Combination analgesics may be comparable to NSAIDs in reducing the pain associated with acute MSK injury.<193,194> The relative risk/benefit ratio for NSAIDs compared to acetaminophen plus codeine in acute soft-tissue disorders is unclear.
4. Skeletal muscle relaxants are not recommended for use in acute soft-tissue disorders. The analgesic efficacy of muscle relaxants as compared to acetaminophen, NSAIDs or combination analgesics is not known. <199,200> Furthermore, the muscle relaxants are associated with a high incidence of CNS impairment that precludes their routine use.
5. Early mobilization and rehabilitation increase strength and decrease the risk of subsequent injuries.<180>
6. There is no evidence to support the routine use of other therapeutic modalities such as ultrasound, TENS and diathermy in acute MSK injury.<25,181>

Section VI

Acute Low Back Pain

SECTION VI: ACUTE LOW BACK PAIN

6.1 Overview

Low back pain is a symptom, rather than a diagnosis, and a precise pathophysiologic cause in most cases is not found. Almost all adults experience this type of nonspecific low back pain at some time in their life. Low back symptoms can lead to activity intolerance and disability. In the United States, low back symptoms are the most common cause of disability for persons less than 45 years of age.<201>

The three-phase model of low back pain is based on the shape of a curve that depicts the proportion of patients still off work at various times after onset of back pain.<202> The acute phase is considered to include up to 4 weeks after the onset of symptoms. The subacute phase is generally 4-12 weeks after the onset of symptoms, while the chronic phase of low back pain is defined as disability for greater than 3 months.<202> The focus of this section is on management of the acute and subacute phases.

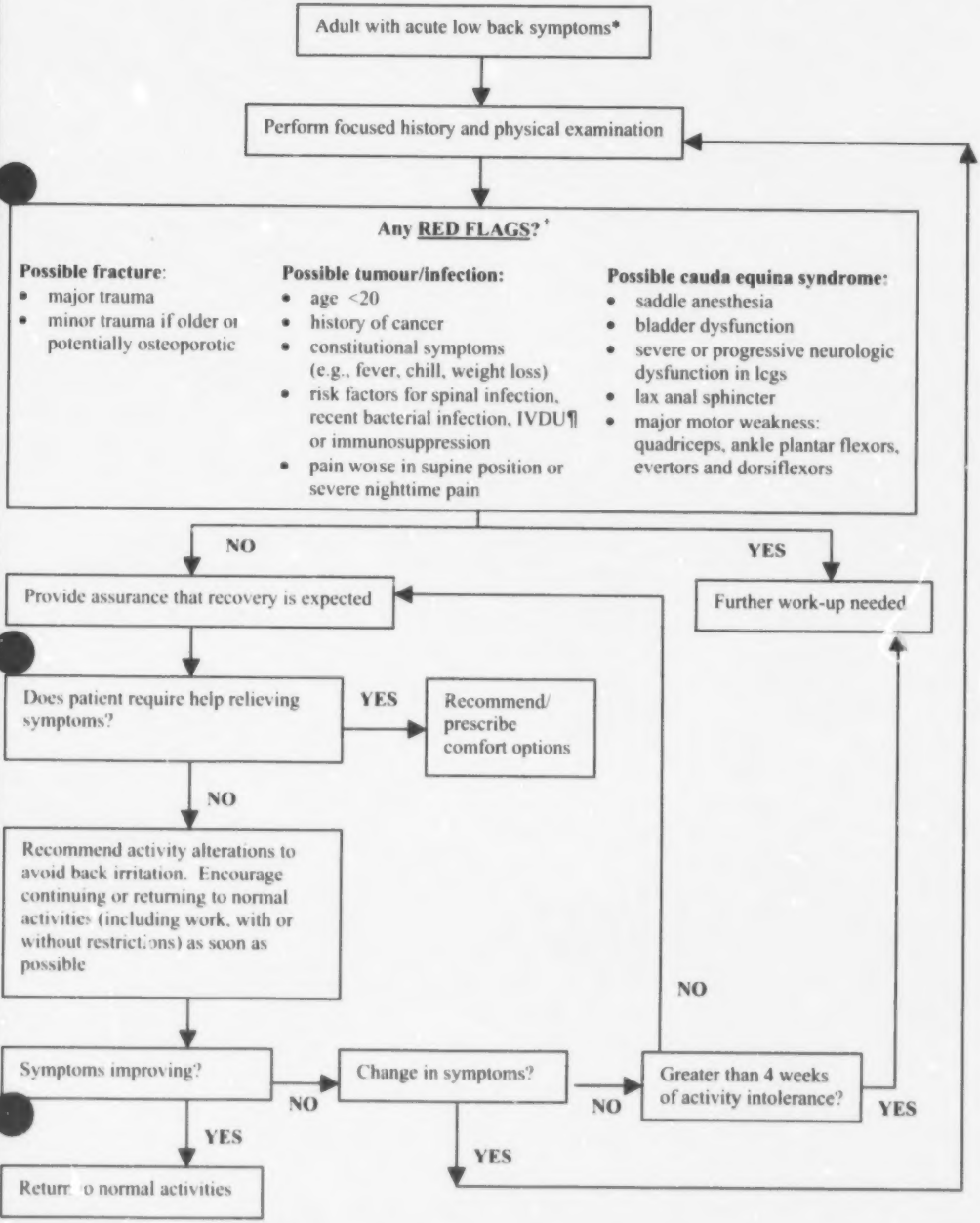
6.2 Management of Acute Low Back Pain

(see Figure 2)

The initial assessment of a patient presenting with low back pain involves a focused medical history and physical examination to rule out serious underlying spinal conditions, such as fracture, tumour, infection or cauda equina syndrome. Diagnostic tests such as x-ray or computerized tomography (CT) are not indicated during the first 4 weeks of low back symptoms unless a patient presents with a "red flag" indicating potentially serious pathology.<201> Psychologic and socioeconomic factors may influence a patient's report of symptoms and treatment outcomes.

The majority of patients with acute low back pain symptoms improve considerably with little or no intervention within one month of symptom onset.<201,203> Milder symptoms or discomfort may persist for 1-3 months in 66-75% of patients.<203>

Figure 2: Algorithm for Management of Acute Low Back Pain (Adapted from <201>)


Adult with acute low back symptoms*
Perform focused history and physical examination
Any RED FLAGS?†
Possible fracture:
major trauma
minor trauma if older or potentially osteoporotic
Possible tumour/infection:
age <20
history of cancer
constitutional symptoms (e.g., fever, chill, weight loss)
risk factors for spinal infection, recent bacterial infection, IVDU¶ or immunosuppression
pain worse in supine position or severe nighttime pain
Possible cauda equina syndrome:
saddle anesthesia
bladder dysfunction
severe or progressive neurologic dysfunction in legs
lax anal sphincter
major motor weakness: quadriceps, ankle plantar flexors, evertors and dorsiflexors
NO
YES
Provide assurance that recovery is expected
Further work-up needed
Does patient require help relieving symptoms?
YES
Recommend/ prescribe comfort options
NO
Recommend activity alterations to avoid back irritation. Encourage continuing or returning to normal activities (including work, with or without restrictions) as soon as possible
NO
Symptoms improving?
NO
Change in symptoms?
NO
Greater than 4 weeks of activity intolerance?
YES
YES
YES
Return to normal activities

* Defined as low back pain or back-related leg symptoms of < 3 months duration leading to activity intolerance
† In the absence of any 'red flags', diagnostic testing is not clinically helpful in the first 4 weeks of symptoms
¶ IVDU = intravenous drug use

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

micromedia
a division of IHS Canada

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

6.2.1 Nonpharmacologic Therapy

A wide variety of non-pharmacologic interventions have been advocated for the treatment of acute low back pain, including: bed rest, patient education (back schools, information pamphlets), passive modalities (heat and/or cold therapy, short wave diathermy, massage, ultrasound), transcutaneous electrical nerve stimulation (TENS), biofeedback, acupuncture, spinal manipulation and early exercise instruction.

Bed rest, even when limited to < 2 days, can delay patient recovery and may lead to debilitation.<204,205> Evidence on the efficacy of back schools (structured patient education in the workplace) is contradictory and therefore is not routinely recommended.<206> Educational pamphlets about low back symptoms do not appear to improve clinical outcomes (symptoms, function or healthcare use) but can improve patient satisfaction with care.<207> Passive modalities, TENS therapy, biofeedback and acupuncture are not supported by the evidence.<25,201,205,208>.

Exercise programs for acute low back pain reported in the literature are quite varied, but most commonly focus on specific back exercises, abdominal exercises, back flexion, back extension, stretching, aerobic exercises (walking, swimming or biking) or some combination of these. The efficacy of these different programs has been difficult to determine <201,209> It appears that back flexion exercise is no more effective than continuing ordinary activities.<202,204> In theory, preventing debilitation due to inactivity and improving activity tolerance may best be achieved by low-stress, aerobic exercises started in the first 2 weeks of symptom onset, followed later by conditioning exercises for trunk muscles.<201>

There is evidence that spinal manipulation and physical therapy (using the Mackenzie method) are minimally more effective than placebo or education alone, but are much more expensive. <201,205,210,211>

6.2.2 Pharmacologic Therapy

Since the majority of patients with acute low back pain symptoms improve within one month of symptom onset, <203> drug therapy is aimed at relieving patient discomfort in the acute phase of symptoms.<201>

Acetaminophen (maximum dose 4g/day) is a reasonable first choice for providing analgesia in acute low back pain, based on its benefit: risk profile. Efficacy data on acetaminophen has been extrapolated from postoperative pain models.<182>

For pain relief in acute low back pain, acetaminophen is recommended as the analgesic of choice.

This is a Grade D recommendation.

NSAIDs provide short-term pain relief for acute low back pain, when compared to placebo.<205,212,213> However, NSAID therapy does not appear to be effective for those patients who have low back pain with sciatica.<214,215>

NSAIDs are recommended as effective short term analgesics for acute low back pain but not sciatica.

This is a Grade B recommendation.

Combination analgesics (e.g. acetaminophen with codeine) have not been compared to placebo in acute low back pain. Two small RCTs suggest that combination analgesics are comparable to NSAIDs for relieving pain in patients with acute low back pain. <194,216>

Combination analgesics provide short-term analgesia in acute low back pain. They may be indicated if plain acetaminophen or NSAIDs are ineffective.

This is a Grade B recommendation.

Skeletal muscle relaxants are not recommended for routine use in acute low back pain. Although these agents have been shown to be superior to placebo for reducing low back pain and improving functional capacity in the short term, muscle relaxants also cause significant adverse effects, such as dizziness (28-36%) and drowsiness (31-49%).<205,217-226> These agents have sedative properties that can impair psychomotor function and driving skills, especially in the elderly.<196>

Skeletal muscle relaxants are not recommended because of limited evidence of efficacy and concern regarding psychomotor impairment.

This is a Grade D recommendation.

6.2.1 Nonpharmacologic Therapy

A wide variety of non-pharmacologic interventions have been advocated for the treatment of acute low back pain, including: bed rest, patient education (back schools, information pamphlets), passive modalities (heat and/or cold therapy, short wave diathermy, massage, ultrasound), transcutaneous electrical nerve stimulation (TENS), biofeedback, acupuncture, spinal manipulation and early exercise instruction.

Bed rest, even when limited to < 2 days, can delay patient recovery and may lead to debilitation.<204,205> Evidence on the efficacy of back schools (structured patient education in the workplace) is contradictory and therefore is not routinely recommended.<206> Educational pamphlets about low back symptoms do not appear to improve clinical outcomes (symptoms, function or healthcare use) but can improve patient satisfaction with care.<207> Passive modalities, TENS therapy, biofeedback and acupuncture are not supported by the evidence.<25,201,205,208>.

Exercise programs for acute low back pain reported in the literature are quite varied, but most commonly focus on specific back exercises, abdominal exercises, back flexion, back extension, stretching, aerobic exercises (walking, swimming or biking) or some combination of these. The efficacy of these different programs has been difficult to determine <201,209> It appears that back flexion exercise is no more effective than continuing ordinary activities.<202,204> In theory, preventing debilitation due to inactivity and improving activity tolerance may best be achieved by low-stress, aerobic exercises started in the first 2 weeks of symptom onset, followed later by conditioning exercises for trunk muscles.<201>

There is evidence that spinal manipulation and physical therapy (using the Mackenzie method) are minimally more effective than placebo or education alone, but are much more expensive. <201,205,210,211>

6.2.2 Pharmacologic Therapy

Since the majority of patients with acute low back pain symptoms improve within one month of symptom onset, <203> drug therapy is aimed at relieving patient discomfort in the acute phase of symptoms.<201>

Acetaminophen (maximum dose 4g/day) is a reasonable first choice for providing analgesia in acute low back pain, based on its benefit: risk profile. Efficacy data on acetaminophen has been extrapolated from postoperative pain models.<182>

For pain relief in acute low back pain, acetaminophen is recommended as the analgesic of choice.

This is a Grade D recommendation.

NSAIDs provide short-term pain relief for acute low back pain, when compared to placebo.<205,212,213> However, NSAID therapy does not appear to be effective for those patients who have low back pain with sciatica.<214,215>

NSAIDs are recommended as effective short term analgesics for acute low back pain but not sciatica.

This is a Grade B recommendation.

Combination analgesics (e.g. acetaminophen with codeine) have not been compared to placebo in acute low back pain. Two small RCTs suggest that combination analgesics are comparable to NSAIDs for relieving pain in patients with acute low back pain. <194,216>

Combination analgesics provide short-term analgesia in acute low back pain. They may be indicated if plain acetaminophen or NSAIDs are ineffective.

This is a Grade B recommendation.

Skeletal muscle relaxants are not recommended for routine use in acute low back pain. Although these agents have been shown to be superior to placebo for reducing low back pain and improving functional capacity in the short term, muscle relaxants also cause significant adverse effects, such as dizziness (28-36%) and drowsiness (31-49%).<205,217-226> These agents have sedative properties that can impair psychomotor function and driving skills, especially in the elderly.<196>

Skeletal muscle relaxants are not recommended because of limited evidence of efficacy and concern regarding psychomotor impairment.

This is a Grade D recommendation.

Table 10: Drug Therapy for Acute Low Back Pain

Agent	Evidence	Usual Dose	Cost	Comments
First-Line Therapy				
Acetaminophen	<182>	325 mg qid prn - 1000 mg qid	$ 0.05 - $0.12	***Effective analgesia demonstrated in postoperative pain models. Toxicity profile more favourable than NSAIDs.***
Second-Line Therapy				
NSAIDs	<205,212-215>	See Table 4	See Table 4	***Superior to placebo for short-term low back pain relief but not for sciatica. All NSAIDs have comparable efficacy in low back pain therapy.***
Combination analgesics (e.g. acetaminophen with codeine)	<194,216>	codeine dose: 60 mg bid – qid prn	$ 0.17 – $ 0.23	***No placebo controlled trials to support use in low back pain. Comparable efficacy to NSAIDs for low back pain relief and functional improvement.***

Notes:

1. **Acetaminophen**
- Clinically significant drug interactions include: warfarin<126>, ethanol<32> and perhaps phenytoin.<32> Maximum doses of acetaminophen may be lower in patients with serious liver or kidney disease.

2. **NSAIDs**
- Clinically significant drug interactions include: lithium, warfarin and methotrexate (rare).<32><127> NSAIDs are associated with a mild increase in supine blood pressure.<92>
- Patients at high-risk for GI bleeding should avoid NSAID use. High-risk is defined primarily by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAIDs can not be avoided, high-risk patients should also receive misoprostol or a proton pump inhibitor <38,41-47,128> or a COX-2 NSAID considered . Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
- Informing patients of the risks has been associated with a lower incidence of acute GI bleeding.<129>
- Avoid in patients with history of ASA hypersensitivity.<93>

3. **Combination analgesics**
- May cause sedation and increase risk of falling and fracture in the elderly.<130>
- Acetaminophen with codeine causes significantly more dizziness, nausea, vomiting and constipation than acetaminophen alone.<122>

Table 10: Drug Therapy for Acute Low Back Pain

Agent	Evidence	Usual Dose	Cost	Comments
First-Line Therapy				
Acetaminophen	<182>	325 mg qid prn - 1000 mg qid	$ 0.05 - $0.12	***Effective analgesia demonstrated in postoperative pain models. Toxicity profile more favourable than NSAIDs.***
Second-Line Therapy				
NSAIDs	<205,212-215>	See Table 4	See Table 4	***Superior to placebo for short-term low back pain relief but not for sciatica. All NSAIDs have comparable efficacy in low back pain therapy.***
Combination analgesics (e.g. acetaminophen with codeine)	<194,216>	codeine dose: 60 mg bid – qid prn	$ 0.17 – $ 0.23	***No placebo controlled trials to support use in low back pain. Comparable efficacy to NSAIDs for low back pain relief and functional improvement.***

Notes:

1. **Acetaminophen**
   - Clinically significant drug interactions include: warfarin<126>, ethanol<32> and perhaps phenytoin.<32> Maximum doses of acetaminophen may be lower in patients with serious liver or kidney disease.
2. **NSAIDs**
   - Clinically significant drug interactions include: lithium, warfarin and methotrexate (rare).<32><127> NSAIDs are associated with a mild increase in supine blood pressure.<92>
   - Patients at high-risk for GI bleeding should avoid NSAID use. High-risk is defined primarily by a history of peptic ulcer disease or GI bleeding, further increased by the addition of advanced age or cardiovascular disease.<38> If NSAIDs can not be avoided, high-risk patients should also receive misoprostol or a proton pump inhibitor <38,41-47,128> or a COX-2 NSAID considered . Women of child-bearing potential prescribed misoprostol should use an effective method of birth control due to the drug's abortifacient and teratogenic potentials.<51>
   - Informing patients of the risks has been associated with a lower incidence of acute GI bleeding.<129>
   - Avoid in patients with history of ASA hypersensitivity.<93>
3. **Combination analgesics**
   - May cause sedation and increase risk of falling and fracture in the elderly.<130>
   - Acetaminophen with codeine causes significantly more dizziness, nausea, vomiting and constipation than acetaminophen alone.<122>

6.3 Acute Low Back Pain Bottom Lines

1. The majority of patients with acute low back pain symptoms improve considerably with little or no intervention within one month of symptom onset.<201,203>
2. Drug therapy is aimed at relieving patient discomfort in the acute phase of symptoms. Acetaminophen (max. dose 4g/d) is the analgesic of choice to relieve acute low back symptoms.
3. NSAIDs are effective in reducing pain in patients with acute low back pain but not acute sciatica. Different NSAIDs appear to be equally effective.<205,212>
4. There are no trials that compare combination analgesics (e.g. acetaminophen with codeine) to placebo. Combination analgesics may be comparable to NSAIDs in reducing low-back pain symptoms.<194> The relative risk/benefit ratio for NSAIDs compared to acetaminophen plus codeine in acute low back pain is unclear <216>
5. Skeletal muscle relaxants are not recommended for routine use in acute low back pain symptoms because of the significant CNS impairment they cause. Although muscle relaxants are more effective than placebo in symptom relief, it is unclear if these agents are comparable to acetaminophen, NSAIDs or combination analgesics.
6. Bed rest, even when limited to <2 days duration, can delay patient recovery and may lead to debilitation.<204,205> Few non-pharmacological therapies are effective in changing longer-term outcomes such as pain and functional status.<202,204,207>
7. Chiropractic spinal manipulation and physiotherapy (Mackenzie method) are minimally more effective than placebo or education alone but are much more expensive.<205,210,211>

Appendices

Appendix A

Core Review Panel Members

Dr. Mary Bell, Rheumatology
Sunnybrook Health Sciences Centre, Toronto

Dr. Tom Bell, Family Medicine
Chemong Region Medical Centre, Bridgenorth

Dr. Claire Bombardier, Rheumatology
Institute for Work and Health, Toronto

Ms. Marie Chambers, Pharmacist
York County Hospital, The Arthritis Program, Newmarket

Dr. Mario Ciccone, Family Medicine
Pine Plaza Medical Centre, Timmins

Dr. Mike Evans, Family Medicine,
Toronto Hospital, Toronto

Dr. Richard Glazier, Family Medicine,
St. Michael's Hospital, Toronto

Dr. Anne Holbrook (Chair),
Clinical Pharmacology/ Internal Medicine/Clinical Epidemiology
Centre for Evaluation of Medicines, Hamilton

Ms. Eileen Nagels, Consumer Representative
The Arthritis Society, Mississauga

Dr. Janet Pope, Rheumatology
London Health Sciences Centre, London

Dr Anita Rao, Family Medicine
St. George Health Centre, Toronto

Dr. Mona Sabharwal, Pharmacist
Vancouver

Dr. Eric Trepanier, Pharmacist
Global Health Consulting Inc., Toronto

Dr. George Wells, Epidemiology
Department of Epidemiology and Community Medicine,
University of Ottawa, Ottawa

Members of Consensus Panel

Members of Core Review Panel plus:

Dr. Ann Cranney, Rheumatology
Ottawa Civic Hospital, Ottawa

Dr. Hui Lee, Internal Medicine
The Group Health Centre, Sault Ste.Marie

Dr. Carter Thorne, Rheumatology
Canadian Rheumatology Association, Newmarket

Dr. Tanveer Towheed, Rheumatology
Queens University, Kingston

External Peer Reviewers Who Provided Feedback Regarding Document

Individuals: physicians, pharmacists, arthritis group representatives

Dr. Jonathan Adachi	Hamilton
Dr. Tassos Anastassiades	Kingston
Dr. Elizabeth Badley	Toronto
Dr. David Bell	London
Dr. Nicholas Bellamy	London
Dr. William Bensen	Hamilton
Dr. Fernando Bianchi	Hamilton
Dr. Arthur Bookman	Toronto
Dr. Sylvie Brule	Ottawa
Dr. Alfred Cividino	Hamilton
Ms. Rita DeSumma	Sault Ste. Marie
Dr. Adel Fam	Toronto
Dr. Peter Ford	Ancaster
Dr. Brian Gamble	Chatham
Dr. Dafna Gladman	Toronto
Dr. Gordon Hardacre	Toronto
Dr. Lawrence Hart	Hamilton
Dr. Robert Inman	Toronto
Dr. Elzbieta Kaminska	Hamilton
Dr. Walter Kean	Hamilton
Dr. Karim Keshavjee	Mississauga
Dr. Peter Lee	Toronto
Dr. Mitchell Levine	Hamilton
Ms. Lyn Maguire	Toronto
Dr. Michael Motyer	Bridgenorth
Dr. Gary Naglie	Toronto

Ms. Mea Renahan	Toronto
Dr. Tulio Scocchia	Hamilton
Dr. Rolf Sebaldt	Hamilton
Dr. John Stewart	Port Perry
Dr. Ronald Willer	London
Ms. Wendy Wong	Toronto

Associations/Governments

The Arthritis Society
Canadian Pharmacists Association
Canadian Rheumatology Association
Canadian Society for Clinical Pharmacology
The Ontario College of Family Physicians
Ontario Medical Association
Ontario Ministry of Health and Long – Term Care, Drug Programs Branch
Ontario Pharmacists' Association
Ontario Program for Optimal Therapeutics
Pharmaceutical Manufacturer's Association of Canada

Pharmaceutical Manufacturers

Bayer Inc.
Boehringer-Ingleheim
Hoechst-Marion Roussel
McNeil Consumer Healthcare
Merck Frosst Canada & Co.
Novartis Pharmaceutical Canada
Purdue, Frederick
Searle, Canada
SmithKline Beecham
Wyeth-Ayerst Canada Inc.

A draft of the guidelines was forwarded to more than 50 other key physicians for their consideration.

Appendix B

The Arthritis Society: Contact Information

The Arthritis Society offers a wide variety of direct help and self-help programs.

Arthritis – Phone Help 1-800-321-1433
A nation-wide, toll free line to provide people with arthritis direct help for their questions concerning any arthritis-related matter.

Arthritis Self-Management Program (ASMP)
A six-week, intensive, self-help program designed to teach people with arthritis how to take an active role in managing their arthritis. Sessions of 10-14 people meet once a week with a trained volunteer, most of who also have arthritis. Each session is about 2 hours long.

Consultation and Rehabilitation Services
A community-based service covering 95% of the province. Trained therapists provide a range of therapeutic, direct treatment, education and counseling services at home, school and the workplace. Funded by the Ontario Ministry of Health and Long - Term Care, there is no charge for the service.

Multi-lingual Education Pamphlets
Free-upon-request pamphlets giving information on topics such as exercise, dealing with stress and controlling pain.

Arthritis News (English) / Arthro-Express (French) magazine
A quarterly journal featuring articles on special interests and therapies for people with arthritis.

People with Arthritis Can Exercise (PACE)
A self-help program teaching ways to use exercise to combat pain.

Other programs and services detailed here are also available. For further information the Society can be reached at:

1-800-321-1433 or http://www.arthritis.ca

Reference List

Reference List

1. Badley EM, Rasooly I, Webster GK. Relative importance of musculoskeletal disorders as a cause of chronic health problems, disability, and health care utilization: findings from the 1990 Ontario Health Survey. Journal of Rheumatology. 1994;21:505-14.
2. Badley EM. The economic burden of musculoskeletal disorders in Canada is similar to that for cancer, and may be higher. Journal of Rheumatology. 1995;22:204-6.
3. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis & Rheumatism. 1998;41:778-99.
4. Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis & Rheumatism. 1996;39:1-8.
5. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part I. Osteoarthritis of the hip.American College of Rheumatology. Arthritis & Rheumatism. 1995;38:1535-40.
6. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee.American College of Rheumatology. Arthritis & Rheumatism. 1995;38:1541-6.
7. Guidelines for the management of rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis & Rheumatism. 1996;39:713-22.
8. Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S. Grades of recommendation for antithrombotic agents. Chest. 1998;114:441s-4s.
9. Tugwell P, Dennis DT, Weinstein A, et al. Laboratory evaluation in the diagnosis of Lyme disease. Ann.Intern.Med. 1997;127:1109-23.
10. Nichol G, Dennis DT, Steere A, et al. Test-treatment strategies for patients suspected of having Lyme disease: A cost-effectiveness analysis. Ann.Intern.Med. 1998;128:37-48.
11. Phillips A, Polisson RP. The rational initial clinical evaluation of the patient with musculoskeletal complaints. Am J Med. 1997;103:7S-11S.
12. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicentre criteria committee. Arthritis & Rheumatism. 1990;33:160-72.
13. Hawker G. Epidemiology of arthritis and osteoporosis. In: Williams J, Badley EM, eds.Patterns of Health Care in Ontario: Arthritis and Related Conditions. Toronto: ICES, 1998:1-10.
14. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Arthritis & Rheumatism. 1986;29:1039-49.
15. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis & Rheumatism. 1991;34:505-14.
16. Puett DW, Griffin MR. Published trials of nonmedicinal and noninvasive therapies for hip and knee osteoarthritis. Ann.Intern.Med. 1994;121:133-40.
17. Ettinger WH, Burns R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The fitness arthritis and seniors trial [FAST]. JAMA. 1997;227:25-31.

18. Kovar PA, Allegrante JP, MacKenzie CR, et al. Supervised fitness walking in patients with osteoarthritis of the knee. A randomized, controlled trial. Ann.Intern.Med. 1992;116:529-34.
19. Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. Ann Intern Med. 1999;132:173-81.
20. Lorig KR, Mazonson PD, Holman HR. Evidence suggesting that health education for self-management in patients with chronic arthritis has sustained health benefits while reducing health care costs. Arthritis & Rheumatism. 1993;36:439-46.
21. Lorig K, Lubeck D, Kraines RG, Seleznick M, Holman HR. Outcomes of self-help education for patients with arthritis. Arthritis & Rheumatism. 1985;28:680-5.
22. Weinberger M, Tierney WM, Booher P, Katz BP. Can the provision of information to patients with osteoarthritis improve functional status? A randomized, controlled trial. Arthritis & Rheumatism. 1989;32:1577-83.
23. Weinberger M, Tierney WM, Cowper PA, Katz BP, Booher PA. Cost-effectiveness of increased telephone contact for patients with osteoarthritis. A randomized, controlled trial. Arthritis & Rheumatism. 1993;36:243-6.
24. Mazzuca SA, Brandt KD, Katz BP, Chambers M, Byrd D, Hanna M. Effects of self-care education on the health status of inner-city patients with osteoarthritis of the knee. Arthritis & Rheumatism. 1997;40:1466-74.
25. Gam AN. Ultrasound therapy in musculoskeletal disorders: a meta-analysis. The Cochrane Library. 1995.
26. Minor MA. Exercise in the management of osteoarthritis of the knee and hip. Arthritis Care & Research. 1994;7:198-204.
27. Ettinger WHJ, Afable RF. Physical disability from knee osteoarthritis: the role of exercise as an intervention. Medicine & Science in Sports & Exercise. 1994;26:1435-40.
28. Amadio Pj, Cummings DM. Evaluation of acetaminophen in the management of osteoarthritis of the knee. Current Therapeutic Research. 1983;34:59-66.
29. Williams HJ, Ward JR, Egger MJ, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis & Rheumatism. 1993;36:1196-206.
30. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N.Engl.J.Med. 1991;325:87-91.
31. O'Grady JG. Paracetamol hepatotoxicity: how to prevent. J R Soc Med. 1997;90:368-70.
32. Crowther R, Holbrook AM, Kenwright R, Kenwright M. Drug interactions among commonly used medications. Chart simplifies data from critical literature review. Canadian Family Physician. 1997;43:1972-81.
33. Griffin M, Singh G. FDA Arthritis Advisory Committee: report on 1. Identifiable risk factors for GI bleeding attributable to NSAIDs 2.NSAIDs gastropathy: the ARAMIS experience. 1995;13-90.
34. Griffin MR, Ray WA, Schaffner W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. Ann.Intern.Med. 1988;109:359-63.
35. Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann.Intern.Med. 1991;114:257-63.
36. Singh G, Ramey DR. NSAID induced gastrointestinal complications: the ARAMIS perspective - 1997. The Journal of Rheumatology. 1998;25:8-16.

37. Kirshen A. Use of medication for arthritis and related conditions. In: Badley EM, Williams CA, eds.Patterns of Health Care in Ontario: Arthritis and Related Conditions. Toronto: ICES, 1998:93-110.
38. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann.Intern.Med. 1995;123:241-9.
39. Peterson WL, Cryer B. COX-1-sparing NSAIDs--is the enthusiasm justified? JAMA. 1999;282:1961-3.
40. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. Journal of Internal Medicine. 1994;236:619-32.
41. Elliott SL, Yeomans ND, Buchanan RR, Smallwood RA. Efficacy of 12 months' misoprostol as prophylaxis against NSAID-induced gastric ulcers. A placebo-controlled trial. Scandinavian Journal of Rheumatology. 1994;23:171-6.
42. Graham DY, White RH, Moreland LW, Schubert TT, Katz R, Jaszewski R. Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. Ann.Intern.Med. 1993;119:257-62.
43. Hawkey CJ, Karrasch JA, Szczepanski L. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. N.Engl.J.Med. 1998;338:727-34.
44. Ekstrom P, Carling L, Wetterhus S, Wingren PE. Omeprazole reduces the frequency of gastroduodenal lesions and dyspeptic symptoms during NSAID treatment. Gastroenterology. 1995;108:A87.
45. Ekstrom P, Carling L, Wetterhus S, et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. A Nordic multicentre study. Scandinavian Journal of Gastroenterology. 1996;31:753-8.
46. Scheiman JM, Behler EM, Loeffler KM, Elta GH. Omeprazole ameliorates aspirin-induced gastroduodenal injury. Digestive Diseases & Sciences. 1994;39:97-103.
47. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. N.Engl.J.Med. 1998;338:719-26.
48. Valentini M, Cannizzaro R, Poletti M, et al. Nonsteroidal antiinflammatory drugs for cancer pain: comparison between misoprostol and ranitidine in prevention of upper gastrointestinal damage. Journal of Clinical Oncology. 1995;13:2637-42.
49. Yeomans ND. Omeprazole healed ulcers and maintained remission better than ranitidine. ACP J Club. 1998;9.
50. Koch M, Dezi A, Ferrario F, Capurso I. Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury. A meta-analysis of randomized controlled clinical trials. Archives of Internal Medicine. 1996;156:2321-32.
51. Pastuszak AL, Schuler L, Speck-Martin CE, Coelho KE, Cordello SM, Vargas F. Use of misoprostol during pregnancy and Mobius syndrome in infants. N.Engl.J.Med. 1999;338:1881-5.
52. Carson JL, Strom BL, Morse ML, et al. The relative gastrointestinal toxicity of the nonsteroidal anti-inflammatory drugs. Archives of Internal Medicine. 1987;147:1054-9.
53. Henry D, Lim LL, García RL, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ. 1996;312:1563-6.
54. García RL, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet. 1994;343:769-72.

55. Langman MJ, Weil J, Wainwright P, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:1075-8.
56. Fries JF, Williams CA, Bloch DA. The relative toxicity of nonsteroidal antiinflammatory drugs. Arthritis & Rheumatism. 1991;34:1353-60.
57. Lisse JR. Clinical efficacy and safety of Naprelan vs Naprosyn in the treatment of rheumatoid arthritis. Am J Orthopedics. 1996;25:21-9.
58. Buchanan WW, Kean WF, St-Jean J. Clinical evaluation of a sustained release compared to a standard formulation of tiaprofenic acid (Surgam) in rheumatoid arthritis: a Canadian multicentre study. Journal of Rheumatology. 1991;18:1046-54.
59. Bacon P, Luqmani RA, Bossingham DH, et al. A comparison of two formulations of indomethacin (Flexin Continuous tablets and Indocid capsules) in the treatment of osteoarthritis. Current Medical Research & Opinion. 1990;12:128-34.
60. Bacon P, Luqmani RA, Barry C. A comparison of two formulations of indomethacin (Flexin Continuous tablets and Indocid capsules) in the treatment of rheumatoid arthritis. Current Medical Research & Opinion. 1990;12:121-7.
61. Kaarela K, Lehtinen K, Skinhoj A. The effect of different indomethacin formulations in young and elderly patients: a comparative controlled clinical trial. Current Medical Research & Opinion. 1989;11:427-31.
62. Canadian Multicentre Study Group. Clinical evaluation of a new controlled-release formulation of naproxen in osteoarthritis and rheumatoid arthritis. Current Medical Research & Opinion. 1988;11:16-27.
63. Essigman W, Lambert J, Sheldon P. A comparison of sustained release preparation of tiaprofenic acid with the conventional tablet formulation and a placebo in rheumatoid arthritis. Intl J Clin Pharmac Res. 1987;7:251-7.
64. Le Loet X, Dreiser RL, Le Gros V. Therapeutic equivalence of diclofenac sustained-released 75mg tablets and diclofenac enteric-coated 50mg tablets in the treatment of painful osteoarthritis. Intl J Clin Practice. 1997;51:389-63.
65. Bellamy N, Beaulieu A, Bombardier C. Efficacy and tolerability of enteric-coated naproxen in the treatment of osteoarthritis and rheumatoid arthritis: a double-blind comparison with standard naproxen followed by an open-label trial. Current Medical Research & Opinion. 1992;12:640-51.
66. Lehn OF, Jensen ON, Andersen LA. Enteric-coated and plain naproxen tablets in osteoarthritis;tolerability and efficacy. Eur J Rheum Inflamm. 1992;12:31-6.
67. Khong TK, Downing MEN, Ellis R. The efficacy and tolerability of enteric and non-enteric coated naproxen tablets: a double-blind study in patients with osteoarthritis. Current Medical Research & Opinion. 1991;12:540-6.
68. Glazier R, Steele L. Are topically applied nonsteroidal anti-inflammatory drugs effective and safe? Canadian Family Physician. 1999;45:1690-2.
69. Henry D. Commentary on "Review: Topical nonsteroidal anti-inflammatory drugs are effective and safe for pain." ACP J Club. 1998 Jul-Aug;129:10. Comment on: Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. BMJ. 1998;316:333-8.
70. Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. BMJ. 1998;316:333-8.
71. Chan TY. Potential dangers from topical preparations containing methyl salicylate. Human & Experimental Toxicology. 1996;15:747-50.
72. Yip AS, Chow WH, Tai YT, Cheung KL. Adverse effect of topical methylsalicylate ointment on warfarin anticoagulation: an unrecognized potential hazard. Postgraduate Medical Journal. 1990;66:367-9.

73. Schmidt RJ, deCorres LF. Allergic contact dermatitis from proprietary topical analgesic sprays containing 3-(aminomethyl)-pyridyl salicylate. Dermatologica. 1987;174:272-9.
74. Zesch A. Short and long-term risks of topical drugs. British Journal of Dermatology. 1986;31 Supp 115:63-70.
75. Candy JM, Morrison C, Paton RD, Logan RW, Lawson R. Salicylate toxicity masquerading as malignant hyperthermia. Paediatric Anaesthesia. 1998;8:421-3.
76. Wallace JL. NSAID gastroenteropathy: past, present and future. Canadian Journal of Gastroenterology. 1996;10:451-9.
77. Tannenbaum H, Davis P, Russell AS, et al. An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus. Canadian NSAID Consensus Participants. Canadian Medical Association Journal. 1996;155:77-88.
78. FDA Center for Drug Evaluation and Research (CDER). New Drug Approval Packages 1998, Celebrex/Medical Review(s) Part 9. Available at: http://www.fda.gov/cder/foi/nda/98/20998.htm. 1998.
79. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthrits. A randomized controlled trial. JAMA. 1999;282:1921-8.
80. Hawkey CJ. COX-2 Inhibitors. The Lancet. 1999;353:307-14.
81. FDA's Electronic Freedom of Information Reading Room. CDER 1999 Meeting Transcripts/Minutes/Other Docs. Center for Drug Evaluation and Research (CDER), Arthritis Advisory Committee Meeting. April 20, 1999. Available at:http://www.fda.gov/ohrms/dockets/ac/cder99t.htm#Arthritis. 1999.
82. Laine L, Harper S, Simon T, et al, for the rofecoxib osteoarthritis endoscopy study group. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Gastroenterology. 1999;117:776-83.
83. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA. 1999;282:1929-33.
84. Hunt R, Thomson ABR. Canadian Helicobacter pylori consensus conference. Can J Gastroenterology. 1998;12:31-44.
85. NIH Consensus Conference. Helicobacter pylori in peptic ulcer disease. NIH Consensus Development Panel on Helicobacter pylori in Peptic Ulcer Disease. JAMA. 1994;272:65-9.
86. Graham DY, Lidsky MD, Cox AM. Long-term nonsteroidal antiinflammatory drug use and Helicobacter pylori infection. Gastroenterology. 1991;100:1653-7.
87. Chan FKL, Sung JJY, Yung MY, Leung KS, Lee YT. Randomised trial of eradication of Helicobacter pylori before non-steroidal antiinflammatory drug therapy to prevent peptic ulcers. Lancet. 1997;350:975-9.
88. Podolosky DK. Does eradication of H. pylori reduce low dose aspirin induced gastroduodenal injury? Digestive Disease Week. 1997;97AD:3839.
89. Hawkey CJ, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of Helicobacter pylori eradication in patients on non-steroidal antiinflammatory drugs: HELP NSAIDs Study. Helicobacter Eradication for Lesion Prevention. Lancet. 1998;352:1016-21.
90. Blackshear JL, Napier JS, Davidman M, Stillman MT. Renal complications of nonsteroidal antiinflammatory drugs: identification and monitoring of those at risk. Semin.Arthritis Rheum. 1985;14:163-75.
91. Bombardier C, Arif Manuel M. Nonsteroidal antiinflammatory drugs and renal function. ACP J Club. 1991;114:16.
92. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann.Intern.Med. 1994;121:289-300.

93. Guidelines for monitoring drug therapy in rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis & Rheumatism. 1996;39:723-31.
94. Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomised, double-blind, multi-centre study. Pain. 1990;43:309-18.
95. The College of Physicians and Surgeons of Ontario. Evidence-based recommendations for management of chronic non-malignant pain. 2000.
96. Dieppe PA, Sathapatayavongs B, Jones HE, Bacon PA, Ring EF. Intra-articular steroids in osteoarthritis. Rheumatology & Rehabilitation. 1980;19:212-7.
97. Gaffney K, Ledingham J, Perry JD. Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. Ann.Rheum.Dis. 1995;54(5):379-81.
98. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. Semin.Arthritis Rheum. 1997;26:755-70.
99. Friedman DM, Moore ME. The efficacy of intraarticular steroids in osteoarthritis: a double-blind study. Journal of Rheumatology. 1980;7:850-6.
100. Hyaluronan injections for osteoarthritis of the knee. The Medical Letter. 1998;40:
101. Dixon AS, Jacoby RK, Berry H. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. Current Medical Research & Opinion. 1988;11:205-13.
102. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group [published erratum appears in J Rheumatol 1999 May;26(5):1216]. J Rheumatol. 1998;25:2203-12.
103. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology (Oxford). 1999;38:602-7.
104. Grecomoro G, Martorana U, Di Marco C. Intra-articular treatment with sodium hyaluronate in gonarthrosis: a controlled clinical trial versus placebo. Pharmatherapeutica. 1987;5:137-41.
105. Scale D, Wobig M, Wolpert W. Viscosupplementation of osteoarthritis knees with hylan: a treatment schedule study. Current Therapeutic Research. 1994;55:220-32.
106. Adams ME, Atkinson MH, Lussier A, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis & Cartilage. 1995;1-13.
107. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injection of a 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. Ann Intern Med. 1994;53:529-34.
108. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. A one-year double-blind, placeob-controlled study. Arthritis Rheum. 1994;37:521-8.
109. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A meta-analysis. European Journal of Clinical Pharmacology. 1994;46:517-22.
110. Deal CL, Schnitzer TJ, Lipstein E, et al. Treatment of arthritis with topical capsaicin: a double-blind trial. Clinical Therapeutics. 1991;13:383-95.
111. Watson CP. Topical capsaicin as an adjuvant analgesic. J Pain Symptom Manage. 1994;9:425-33.

112. Naylor CD, Williams JI. Primary hip and knee replacement surgery: Ontario criteria for case selection and surgical priority. Quality in Health Care. 1996;5:20-30.
113. Callahan CM, Drake BG, Heck DA, Dittus RS. Patient outcomes following tricompartmental total knee replacement. A meta-analysis. JAMA. 1994;271:1349-57.
114. Towheed T, Hochberg M. Health-related quality of life after total hip replacement. Semin.Arthritis Rheum. 1996;26:483-91.
115. Barclay TS, Tsourounis C, McCart G. Glucosamine. Annals of Pharmacotherapy. 1998;32:574-9.
116. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA. 2000;283:1469-75.
117. Towheed T. Glucosamine sulphate in osteoarthritis: a systematic review. Arthritis & Rheumatism. 1998;41:S198.
118. Towheed TE, Anastassiades TP. Glucosamine and chondroitin for treating symptoms of osteoarthritis: evidence is widely touted but incomplete. JAMA. 2000;283:1483-4.
119. Heller CA, Ingelfinger JA, Goldman P. Nonsteroidal antiinflammatory drugs and aspirin--analyzing the scores. Pharmacotherapy. 1985;5:30-8.
120. Watson MC, Brooke ST, Kirwan JR, Faulkner A. The Comparative Efficacy of Non-Aspirin Non-Steroidal Anti-Inflammatory Drugs for the Management of Osteoarthritis of the Knee: A Systematic Review. Cochrane Library. 1998;1-17.
121. Towheed T, Shea B, Hochberg M. Osteoarthritis: a systematic review of randomized controlled trials of analgesia and anti-inflammatory therapy in osteoarthritis [OA] of the hip. The Cochrane Library- 1998 Issue 1. 1997;1-19.
122. de Craen AJ, Di Giulio G, Lampe-Schoenmaeckers JE, Kessels AG, Kleijnen J. Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. BMJ. 1996;313:321-5.
123. Boissier C, Perpoint B, Laporte-Simitsidis S, et al. Acceptability and efficacy of two associations of paracetamol with a central analgesic (dextropropoxyphene or codeine): comparison in osteoarthritis. Journal of Clinical Pharmacology. 1992;32:990-5.
124. Campion EW. Why unconventional medicine? N.Engl.J.Med. 1993;328:282-3.
125. Listrat V, Ayral X, Patarnello F, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. Osteoarthritis & Cartilage. 1997;5:153-60.
126. Hylek EM, Heiman H, Skates SJ, Sheenan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. JAMA. 1998;279:657-62.
127. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Archives of Internal Medicine. 1993;153:1665-70.
128. Raskin J, White R, Jackson JE, Weaver AL. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens. Ann.Intern.Med. 1995;123:344-50.
129. Wynne HA, Long A. Patient awareness of the adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs). British Journal of Clinical Pharmacology. 1996;42:253-6.
130. Shorr RI, Griffin M, Daughtery JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly:codeine and propoxyphene. J of Gerontology. 1992;47:M111-M115.

131. Chatham W, Williams G, Moreland L, Parker JW, Ross C, Alarcon SG. Intrarticular corticosteroid injections: should we rest the joints? Arthritis Care & Research. 1989;2:70-4.
132. Pincus T. The underestimated long term medical and economic consequences of rheumatoid arthritis. Drugs. 1995;50 Suppl 1:1-14.
133. Mitchell JM, Burkhauser RV, Pincus T. The importance of age, education, and comorbidity in the substantial earnings losses of individuals with symmetric polyarthritis. Arthritis & Rheumatism. 1988;31:348-57.
134. Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. Journal of Rheumatology. 1989;16:585-91.
135. van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis & Rheumatism. 1992;35:26-34.
136. Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis & Rheumatism. 1984;27:864-72.
137. Myllykangas-Luosujarvi RA, Aho K, Isomaki HA. Mortality in rheumatoid arthritis. Semin.Arthritis Rheum. 1995;25:193-202.
138. Symmons DP. Mortality in rheumatoid arthritis. Br.J Rheumatol. 1988;27 Suppl 1:44-54.
139. Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. Arthritis & Rheumatism. 1994;37:481-94.
140. Symmons D. Excess mortality in rheumatoid arthritis--is it the disease or the drugs? Journal of Rheumatology. 1995;22:2200-2.
141. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously--predictive markers, socioeconomic status and comorbidity. Journal of Rheumatology. 1986;13:841-5.
142. Lichtenstein MJ, Pincus T. Rheumatoid arthritis identified in population based cross sectional studies: low prevalence of rheumatoid factor. Journal of Rheumatology. 1991;18:989-93.
143. Suarez-Almazor ME, Soskolne CL, Saunders LD, Russell AS. Use of second line drugs for the treatment of rheumatoid arthritis in Edmonton, Alberta. Patterns of prescription and long-term effectiveness. Journal of Rheumatology. 1995;22:836-43.
144. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis & Rheumatism. 1988;31:315-24.
145. Fries JF, Williams CA, Morfeld D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. Arthritis & Rheumatism. 1996;39:616-22.
146. van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann.Intern.Med. 1996;124:699-707.
147. Egsmose C, Lund B, Borg G, et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. The Journal of Rheumatology. 1995;22:2208-13.
148. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis & Rheumatism. 1993;36:729-40.

149. Goldsmith CH, Boers M, Bombardier C, Tugwell P, for the Omeract Committee. Criteria for clinically important changes in outcomes:development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. Journal of Rheumatology. 1993;20:561-5.
150. Van den Ende CH, Vliet VT, Munneke M, Hazes JM. Dynamic exercise therapy in rheumatoid arthritis: a systematic review. Br.J Rheumatol. 1998;37:677-87.
151. Van den Ende CH, Hazes JM, le Cessie S, et al. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomised clinical trial. Ann.Rheum.Dis. 1996;55:798-805.
152. Fries JF, Carey C, McShane DJ. Patient education in arthritis: randomized controlled trial of a mail-delivered program. Journal of Rheumatology. 1997;24:1378-83.
153. Bell MJ, Lineker SC, Wilkins AL, Goldsmith CH, Badley EM. A randomized controlled trial to evaluate the efficacy of the community based physical therapy in the treatment of people with rheumatoid arthritis. Journal of Rheumatology. 1998;25:231-7.
154. Suarez-Almazor ME, Shea B, Wells G, Tugwell P. Rheumatoid Arthritis (RA): Sulfasalazine Versus Placebo in RA. (Cochrane Review). Cochrane Library. 1997;1-11.
155. Suarez-Almazor ME, Shea B, Homik J, Wells G, Tugwell P. Rheumatoid Arthritis (RA) :Antimalarials Versus Placebo in RA. (Cochrane Review). Cochrane Library. 1997;1-10.
156. Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Rheumatoid Arthritis (RA): Methotrexate Versus Placebo in the treatment of RA. (Cochrane Review). Cochrane Library. 1997;1-11.
157. Wells G, Haguenauer D, Shea B, Suarez-Almazor ME, Welch VA, Tugwell P. Rheumatoid Arthritis (RA) : A Meta-Analysis of Cyclosporine in Rheumatoid Arthritis (Cochrane Review). Cochrane Library. 1998;1-9.
158. ten Wolde S, Breedveld FC, Hermans J, et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. Lancet. 1996;347:347-52.
159. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisone, methotrexate and suplhasalazine with sulphasalazine alone in early rheumatoid arthritis. The Lancet. 1997;350:309-18.
160. Verhoeven AC, Bibo JC, Boers M, Engel GL, van der Linden S, for the COBRA Trial Group. Cost-effectiveness and cost-utility of combination therapy in early rheumatoid arthritis: randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone. Br.J Rheumatol. 1998;37:1102-9.
161. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N.Engl.J.Med. 1996;334:1287-91.
162. Tugwell P, Pincus T, Yocum D, Stein M, Gluck O. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. N.Engl.J.Med. 1995;333:137-41.
163. Mottonen T, Hannonen P, Leirisolo-Repo M, et al, for the FIN-RACo trial group. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. The Lancet. 1999;353:1568-73.
164. Madhok R, Capell HA. Outstanding issues in use of disease-modifying agents in rheumatoid arthritis. The Lancet. 1999;353:257-8.
165. Gotzsche PC, Johansen HK. Meta-analysis of short-term low dose prednisolone versus placebo and non-steroidal anti-inflammatory drugs in rheumatoid arthritis. BMJ. 1998;316:811-8.

166. Criswell LA, Saag KG, Sems KM, et al. Rheumatoid arthritis (RA): moderate-term low dose corticosteroids. Cochrane Library. 1998;1-34.
167. van Vliet-Daskalopoulou E, Jentjens T, Scheffer RT, International Rimexolone Study Group. Intra-articular rimexolone in the rheumatoid knee: a placebo-controlled, double-blind, multicentre trial of three doses. Br.J Rheumatol. 1987;26:450-3.
168. Srinivasan A, Amos M, Webley M. The effects of joint washout and steroid injection compared with either joint washout or steroid injection alone in rheumatoid knee effusion. Br.J Rheumatol. 1995;34:771-3.
169. Gonzales GR, Portenoy RK. Selection of analgesic therapies in rheumatoid arthritis: the role of opioid medications. Arthritis Care & Research. 1993;6:223-8.
170. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. Arthritis & Rheumatism. 1990;33:1449-61.
171. Gotzsche PC. Meta-analysis of NSAIDs: contribution of drugs, doses, trial designs, and meta-analytic techniques. Scandinavian Journal of Rheumatology. 1993;22:255-60.
172. Gotzsche PC, Johansen HK. Rheumatoid Arthritis (RA): Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. (Cochrane Review). Cochrane Library. 1997;1-18.
173. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on Osteoporosis Guidelines. Arthritis & Rheumatism. 1996;39:1791-801.
174. Matteson EL, Hickey AR, Maguire L, Tilson HH, Urowitz MB. Occurence of neoplasia in patients with rheumatoid arthritis enrolled in a DMARD registry. J Rheumatology. 1991;18:809-14.
175. Ortiz Z, Shea B, Suarez Almazor M, Moher D, Wells G, Tugwell P. Rheumatoid Arthritis (RA):The Efficacy of Folic Acid and Folinic Acid Reducing Methotrexate Side Effects in RA. (Cochrane Review). Cochrane Library. 1997;1-15.
176. Lipsky PE, et al. Algorithms for the diagnosis and management of musculoskeletal complaints. The American Journal of Medicine. 1997;103(6A):79S.
177. Calabrese LH, Rooney TW. The use of nonsteroidal anti-inflammatory drugs in sports. The physician and sports medicine. 1986;14:89-97.
178. Arrington ED, Miller MD. Skeletal muscle injuries. Sports Medicine. 1995;26:411-22.
179. Kannus P, Renstrom P. Treatment for acute tears of the lateral ligaments of the ankle. J of Bone & Joint Surgery. 1991;73A:305-12.
180. Watson AS. Running injuries - knees to toes. Australian Family Physician. 1998;17:99-103.
181. Ogilvie-Harris DJ, Gilbart M. Treatment modalities for soft tissue injuries of the ankle: a critical review. Clinical Journal of Sport Medicine. 1995;5:175-86.
182. Li Wan Po A, Zhang WY. Analgesic efficacy of ibuprofen alone and in combination with codeine or caffeine in post-surgical pain: a meta-analysis. European Journal of Clinical Pharmacology. 1998;53:303-11.
183. Bahamonde LA, Saavedra H. Comparison of the analgesic and anti-inflammatory effects of diclofenac potassium versus piroxicam versus placebo in ankle sprain patients. J Int Med Res. 1990;18:104-11.
184. Fitch K, Gray SD. Indomethacin in soft-tissue sports injuries. Med J Aust. 1974;1:260-3.
185. Giani E, Rocchi L, Tavoni A, Montanari M, Garagiola U. Telethermographic evaluation of NSAIDs in the treatment of sports injuries. Medicine & Science in Sports & Exercise. 1989;21:1-6.

186. Slayter MA, Hensley MJ, Lopert R. A randomized controlled trial of piroxicam in the management of acute ankle sprain in Australian regular army recruits. Amer J of Sports Med. 1997;25:544-53.
187. Lereim P, Gabor I. Piroxicam and naproxen in acute sports injuries. The Amer J of Med. 1988;84:45-9.
188. Moran M. Double-blind comparison of diclofenac potassium, ibuprofen and placebo in the treatment of ankle sprains. J Int Med Res. 1991;19:121-30.
189. Moran M. An observer-blind comparison of diclofenac potassium, piroxicam and placebo in the treatment of ankle sprains. Current Medical Research & Opinion. 1990;12:268-74.
190. Santilli G, Tuccimei U, Cannistra FM. Comparative study with piroxicam and ibuprofen vs placebo in the supportive treatment of minor sports injuries. J Int Med Res. 1980;8:265-9.
191. Sloan JP, Hain R. Benefits of early anti-inflammatory medication following acute ankle injury. Injury. 1989;20:81-3.
192. Van Heerden JJ. Diclophenac sodium, oxyphenbutazone and placebo in sports injuries of the knee. S A Medical Journal. 1977;396-9.
193. Jaffe GV, Roylance PJ, Grimshaw JJ. A controlled study of diflunisal in sprains and strains. Current Medical Research & Opinion. 1978;5:584-8.
194. Muncie H, King DE, DeForge B. Treatment of mild to moderate pain of acute soft tissue injury:diflunisal vs acetaminophen with codeine. J of Fam Practice. 1986;23:125-7.
195. Indelicato PA. Comparison of diflusinal and acetaminophen with codeine in the treatment of mild to moderate pain due to strains and sprains. Clinical Therapeutics. 1986;8:269-73.
196. Ray WA, Thapa PB, Shorr RI. Day LK, ed. Medications and the older driver. Philadelphia: W.B. Saunders Co., 1993:413-37.
197. Dupont M, Beliveau P, Theriault G. The efficacy of anti-inflammatory medication in the treatment of the acutely sprained ankle. Amer J of Sports Med. 1987;15:41-5.
198. Huskisson EC, Berry H, Street FG, Medhurst HE. Indomethacin for soft-tissue injuries. A double-blind study in football players. Rheumatology & Rehabilitation. 1973;12:159-60.
199. Gilbert MM, Koepke HH. Relief of musculoskeletal and associated psychopathological symptoms with meprobamate and aspirin: a controlled study. Current Therapeutic Research, Clinical & Experimental. 1973;15:820-32.
200. Tisdale SAJ, Ervin DK. A controlled study of methocarbamol (Robaxin) in acute painful musculoskeletal conditions. Current Therapeutic Research, Clinical & Experimental. 1975;17:525-30.
201. Bigos S, Bowyer O, Braen G. Acute low back problems in adults. Clinical practice guideline no.14. AHCPR publication no. 95-0642. 98 A.D.
202. Frank j, Sinclair S, Hogg-Johnson S, et al. Preventing disability from work-related low-back pain. Canadian Medical Association Journal. 1998;158:1625-31.
203. Von Korff M, Saunders K. The course of back pain in primary care. Spine. 1996;21:2833-9.
204. Malmivaara A, Hakkinen U, Heinrichs M, et al. The treatment of acute low back pain - bed rest, exercises, or ordinary activity? N.Engl.J.Med. 1995;332:351-5.
205. van Tulder MW, Koes BW, Bouter LM. Conservative treatment of acute and chronic nonspecific low back pain: a systematic review of randomized controlled trials of the most common interventions. Spine. 1997;15:21-128.
206. Koes BW, van Tulder MW, Van der Windt WM, Bouter LM. The efficacy of back schools: a review of randomized clinical trials. J Clin Epidemiol. 1994;47:851-62.

207. Cherkin DC, Deyo RA, Street JH, Hunt M, Barlow W. Pitfalls of patient education. Limited success of a program for back pain in primary care. Spine. 1996;21:345-55.
208. Tulder MW, Cherkin DC, Berman B, Koes BW. The effectiveness of acupuncture in the treatment of low back pain. The Cochrane Library. 1999;1-16.
209. Koes BW, Bouter LM, Beckerman H, van der Heijden GM, Knipschild PG. Physiotherapy exercises and back pain: a blinded review. BMJ. 1991;302:1572-6.
210. Cherkin DC, Deyo RA, Battie M, Street JH. A comparison of physical therapy, chiropractic manipulation, and provision of an educational booklet for the treatment of patients with low back pain. N.Engl.J.Med.. 1998;339:1021-9.
211. Koes BW, Assendelft WJJ, van der Heijden GM, Bouter LM, Knipschild PG. Spinal manipulation and mobilisation for back and neck pain: a blinded review. BMJ. 1991;303:1298-303.
212. Koes BW, Scholten JPM, Mens JMA, Bouter LM. Efficacy of non-steroidal anti-inflammatory drugs for low back pain: a systematic review of randomised clinical trials. Ann Rheum Dis. 1997;56:214-23.
213. Amlie E, Weber H, Holme I. Treatment of acute low-back pain with piroxicam: results of a double-blind placebo-controlled trial. Spine. 1987;12:473-6.
214. Goldie I. A clinical trial with indomethacin (indomee) in low back pain and sciatica. Acta Orthop Scand. 1968;39:117-28.
215. Weber H, Holme I, Amlie E. The natural course of acute sciatica with a nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroixicam. Spine. 1993;18:1433-8.
216. Brown FLJr, Bodison S, Dixon J, Davis W, Nowoslawski J. Comparison of diflunisal and acetaminophen with codeine in the treatment of initial or recurrent acute low back strain. Clinical Therapeutics. 1986;9:52-8.
217. Baratta RR. A double-blind comparative study of carisoprodol, propoxyphene, and placebo in the management of low back syndrome. Current Therapeutic Research, Clinical & Experimental. 1976;20:233-40.
218. Baratta RR. A double-blind study of cyclobenzaprine and placebo in the treatment of acute musculoskeletal conditions of the low back. Current Therapeutic Research. 1982;32:646-52.
219. Basmajian JV. Acute back pain and spasm. A controlled multicenter trial of combined analgesic and antispasm agents. Spine. 1989;14:438-9.
220. Dapas F, Hartman SF, Martinez L, et al. Baclofen for the treatment of acute low-back syndrome. A double-blind comparison with placebo. Spine. 1985;10:345-9.
221. Hindle TH. Comparison of carisoprodol, butabarbital, and placebo in treatment of the low back syndrome. California Medicine. 1972;117:7-11.
222. Hoivik HO, Moe N. Effect of a combination of orphenadrine/paracetamol tablets ('Norgesic') on myalgia: a double-blind comparison with placebo in general practice. Current Medical Research & Opinion. 1983;8:531-5.
223. Valtonen EJ. A controlled clinical trial of chlormezanone, orphenadrine, orphenadrine/paracetamol and placebo in the treatment of painful skeletal muscle spasms. Annals of Clinical Research. 1975;7:85-8.
224. Walker JM. Value of an acetaminophen-chlorzoxazone combination (parafon forte) in the treatment of acute musculoskeletal disorders. Current Therapeutic Research, Clinical & Experimental. 1973;15:248-52.
225. Boyles WF, Glassman JM, Soyka JP. Management of acute musculoskeletal conditions: Thoracolumbar strain or sprain. Today's Therapeutic Trends. 1983;1:1-16.
226. Casale R. Acute Low Back Pain. Symptomatic treatment with a muscle relaxant drug. Clin J of Pain. 1988;4:81-8.